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(54) Title: A BUILDING BLOCK FORMING A C=C DOUBLE BOND UPON REACTION

(57) Abstract: A building block having the dual capabilities of recognising an encoding element and transferring a Functional Entity Precursor to a recipient reactive group is disclosed. The building block may be used in the generation of a single complex or libraries of different complexes, wherein the complex comprises an encoded molecule linked to an encoding element. Libraries of complexes are useful in the quest for pharmaceutically active compounds.

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Title

A BUILDING BLOCK FORMING A C=C DOUBLE BOND UPON REACTION

Technical Field of the Invention

The present invention relates to a building block comprising a complementing element and a precursor for a functional entity. The building block is designed to transfer the Functional Entity Precursor to a recipient reactive group upon recognition between the complementing element and an encoding element associated with the reactive group.

Background

The transfer of a chemical entity from one mono-, di- or oligonucleotide to another has been considered in the prior art. Thus, N. M. Chung *et al.* (Biochim. Biophys. Acta,1971, 228,536-543) used a poly(U) template to catalyse the transfer of an acetyl group from 3'-O-acetyladenosine to the 5'-OH of adenosine. The reverse transfer, i.e. the transfer of the acetyl group from a 5'-O-acetyladenosine to a 3'-OH group of another adenosine, was also demonstrated.

Walder *et al.* Proc. Natl. Acad. Sci. USA, 1979, 76, 51-55 suggest a synthetic procedure for peptide synthesis. The synthesis involves the transfer of nascent immobilized polypeptide attached to an oligonucleotide strand to a precursor amino acid attached to an oligonucleotide. The transfer comprises the chemical attack of the amino group of the amino acid precursor on the substitution labile peptidyl ester, which in turn results in an acyl transfer. It is suggested to attach the amino acid precursor to the 5' end of an oligonucleotide with a thiol ester linkage.

The transfer of a peptide from one oligonucleotide to another using a template is disclosed in Bruick RK et al. Chemistry & Biology, 1996, 3:49-56. The carboxy terminal of the peptide is initially converted to a thioester group and subsequently transformed to an activated thioester upon incubation with Ellman's reagent. The activated thioester is reacted with a first oligo, which is 5'-thiol-terminated, resulting in the formation of a thio-ester linked intermediate. The first oligonucleotide and a second oligonucleotide having a 3' amino group is aligned on a template such that the thioester group and the amino group are positioned in close proximity and a

transfer is effected resulting in a coupling of the peptide to the second oligonucleotide through an amide bond.

The Wittig reaction (Wittig and Geissler, Liebigs Ann. Chem. (1953), 580, 44) is a well appreciated C=C double bond forming reaction in organic synthesis (Chem. Rev. (1989), 89, 863). The reaction with stabilised phosphonium salts is however limited to reaction with primarily aldehydes and furthermore favour formation of only Z-alkenes. The Horner-Wadsworth-Emmons (HWE) modification of the Wittig reaction provides several advantages. Firstly, the reactive species of stabilised HWE-reagents is more reactive and therefore reacts with a broader range of carbonyl compounds, even hindered ketones (Comprehensive Organic Synthesis, Vol I, p. 762). Secondly, the stereochemical identity of the formed C=C double bond can be controlled by the substituents on the phosphorous atom. Formation of Z-alkenes are favoured by using Stills or Andos HWE-reagents (Still and Gennari, Tetrahedron Lett. (1983), 24, 4405-08, Ando, J. Org. Chem. (1998), 63, 8411-8416), whereas the formation of E-alkenes are favoured using simple alkyl based HWE-reagents (Chem. Rev. (1989), 89, 863).

Summary of the Invention

The present invention relates to a building block of the general formula:

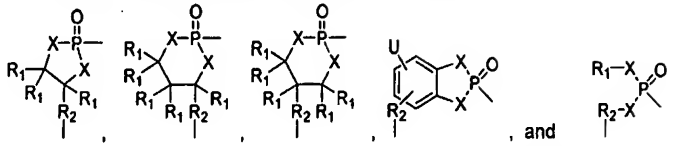
Complementing Element – Linker – Carrier – Functional entity precursor

capable of transferring a functional entity precursor to a recipient reactive group, wherein

Complementing Element is a group identifying the functional entity,

Linker is a chemical moiety comprising a **spacer** and a **S-C-connecting group**, wherein the spacer is a valence bond or a group distancing the functional entity precursor to be transferred from the complementing element and the S-C-connecting group connects the spacer with the Carrier,

Carrier is selected among the groups consisting of



, and

wherein the Functional entity precursor is attached to the phosphorous atom,

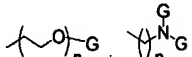
each individual X is chosen independently among the group consisting of NR^{16},O, S, and Se;

U = R^3;

R^1 = H, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl C_2-C_6 alkenyl, C_2-C_6 alkynyl, aryl or heteroaryl; optionally substituted with one or more F, Cl, Br, I, or CN, and where each of the individual R^1 groups are chosen independently;

R^2 = a valence bond, C_1-C_6 Alkylene, C_2-C_6 Alkenylene, C_2-C_6 Alkynylene, Arylene, Heteroarylene, C_1-C_6 Alkylene-arylene or C_1-C_6 Alkylene-heteroarylene;

R^3 is selected from -H, $-OR^4$, $-NR^4_2$, - F, -Cl, -Br, -I, $-NO_2$, -CN, $-C(Halogen)_3$, $-C(O)R^4$, $-C(O)NHR^4$, $C(O)NR^4_2$, $-NC(O)R^4$, $-S(O)_2NHR^4$, $-S(O)_2NR^4_2$, $-S(O)_2R^4$, $-P(O)_2-R^4$, $-P(O)-R^4$, $-S(O)-R^4$, $P(O)-OR^4$, $-S(O)-OR^4$, $-N^+R^4_3$, wherein and each individual R^4 is chosen independently from H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or aryl,

R^{16} is selected independently from H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, aryl, C_1-C_6 alkylene-aryl,  or  , G is H or C_1-C_6 alkyl and n is 1,2,3 or 4.

Functional entity precursor is of the general formula C(H)(V)-W;

wherein V independently is H, alkyl, alkenyl, alkynyl, alkadienyl, cycloalkyl, cycloheteroalkyl, aryl or heteroaryl, optionally substituted with one or more substituents selected from the group consisting of $SnR^5R^6R^7$, $Sn(OR^5)R^6R^7$, $Sn(OR^5)(OR^6)R^7$, BR^5R^6, $B(OR^5)R^6$, $B(OR^5)(OR^6)$, halogen, CN, CNO, $C(halogen)_3$, =O, $=NOR^5$, $=NNR^5R^6$, OR^5, $OC(=O)R^5$, $OC(=O)OR^5$, $OC(=O)NR^5R^6$, SR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$, NO_2, N_3, NR^5R^6, $N^+R^5R^6R^7$, NR^5OR^6, $NR^5NR^6R^7$, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, NC, $P(=O)(OR^5)OR^6$, $P^+R^5R^6R^7$, $C(=O)R^5$, $C(=NR^5)R^6$, $C(=NOR^5)R^6$, $C(=NNR^5R^6)$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$, $C(=O)NR^5NR^6R^7$, $C(=NR^5)NR^6R^7$, $C(=NOR^5)NR^6R^7$ or R^8,

wherein,

R^5, R^6 and R^7 independently is H, alkyl, alkenyl, alkynyl, alkadienyl, cycloalkyl, cycloheteroalkyl, aryl or heteroaryl, optionally substituted with one or more substituents selected from the group consisting of halogen, CN, CNO, $C(halogen)_3$, =O, $=NOR^5$, $=NNR^5R^6$, OR^8, $OC(=O)R^8$, $OC(=O)OR^8$, $OC(=O)NR^8R^9$, SR^8, $S(=O)R^8$, $S(=O)_2R^8$, $S(=O)_2NR^8R^9$, NO_2, N_3, NR^8R^9, $N^+R^8R^9R^{10}$, NR^5OR^6, $NR^5NR^6R^7$, $NR^8C(=O)R^9$, $NR^8C(=O)OR^9$, $NR^8C(=O)NR^9R^{10}$, NC, $P(=O)(OR^8)OR^9$, $P^+R^5R^6R^7$, $C(=O)R^8$, $C(=NR^8)R^9$, $C(=NOR^8)R^9$, $C(=NNR^8R^9)$, $C(=O)OR^8$, $C(=O)NR^8R^9$,

$C(=O)NR^8OR^9$ $C(=NR^5)NR^6R^7$, $C(=NOR^5)NR^6R^7$or $C(=O)NR^6NR^9R^{10}$, wherein R^5 and R^6 may together form a 3-8 membered heterocyclic ring or R^5 and R^7 may together form a 3-8 membered heterocyclic ring or R^6 and R^7 may together form a 3-8 membered heterocyclic ring,

wherein,

R^8, R^9 and R^{10} independently is H, alkyl, alkenyl, alkynyl, alkadienyl, cycloalkyl, cycloheteroalkyl, aryl or heteroaryl and wherein R^8 and R^9 may together form a 3-8 membered heterocyclic ring or R^8 and R^{10} may together form a 3-8 membered heterocyclic ring or R^9 and R^{10} may together form a 3-8 membered heterocyclic ring.

W is selected among the group consisting of H, aryl, heteroaryl, $C(=O)OR^{11}$, $C(O)R^{11}$, $C(=O)NR^{11}{}_2$, $C(=O)NR^{11}OR^{11}$, $C(=NR^{11})OR^{11}$, $C(=NOR^{11})$ R^{11}, $C(=NNR^{11}{}_2)R^{11}$, $S(O)R^{11}$, $S(O)_2R^{11}$, $S(O)NR^{11}{}_2$, $S(O)_2NR^{11}{}_2$, -CN, $P(O)$ $R^{11}{}_2$, $-NO_2$, $NR^{11}{}_3{}^+$ or $SR^{11}{}_2{}^+$

where each individual R^{11} is H or selected independently among the group consisting of C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, aryl, heteroaryl, said group being substituted with 0-3 R^{12} and 0-3 R^{15} and

each individual R^{12} is selected independently from $-N_3$, -CNO, $-C(NOH)NH_2$, $-NHOH$, $-NHR^4NHR^4$, $-C(O)R^4$, $-SnR^4{}_3$, $-B(OR^4)_2$, $-P(O)(OR^4)_2$ or the group consisting of C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_4-C_8 alkadienyl said group being substituted with 0-2 R^{13},

where each individual R^{13} is independently selected from $-NO_2$, $-C(O)OR^{14}$, $-C(O)R^{14}$, -CN, $-OSiR^{14}{}_3$, $-OR^{14}$ and $-NR^{14}{}_2$,

each individual R^{14} is independently chosen from a group comprising H, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_7 cycloalkyl, aryl or C_1-C_8 alkylene-aryl substituted with 0-3 substituents independently selected from $-F$, -Cl, $-NO_2$, $-R^4$, $-OR^4$, $-SiR^4{}_3$,

R^{15} is =O, -F, -Cl, -Br, -I, -CN, $-NO_2$, $-OR^{14}$, $-NR^{14}{}_2$, $-NR^{14}$-$C(O)R^{14}$, $-NR^{14}$-$C(O)OR^{14}$, $-SR^{14}$, $-S(O)$ R^{14}, $-S(O)_2R^{14}$, $-COOR^{14}$, $-C(O)NR^{14}{}_2$ and $-S(O)_2NR^{14}{}_2$.

The term "C_3-C_7 cycloheteroalkyl" as used herein refers to a radical of totally saturated heterocycle like a cyclic hydrocarbon containing one or more heteroatoms selected from nitrogen, oxygen, phosphor, boron and sulphur independently in the cycle such as pyrrolidine (1- pyrrolidine; 2- pyrrolidine; 3- pyrrolidine; 4- pyrrolidine; 5- pyrrolidine); pyrazolidine (1- pyrazolidine; 2- pyrazolidine; 3- pyrazolidine; 4-pyrazolidine; 5-pyrazolidine); imidazolidine (1- imidazolidine; 2- imidazolidine; 3- imidazolidine; 4- imidazolidine; 5- imidazolidine); thiazolidine (2- thiazolidine; 3- thiazolidine; 4- thiazolidine; 5- thiazolidine); piperidine (1- piperidine; 2- piperidine; 3- piperidine; 4- piperidine; 5- piperidine; 6- piperidine); piperazine (1- piperazine; 2- piperazine; 3- piperazine; 4- piperazine; 5- piperazine; 6- piperazine); morpholine (2- morpholine; 3- morpholine; 4- morpholine; 5- morpholine; 6- morpholine); thiomorpholine (2- thiomorpholine; 3- thiomorpholine; 4- thiomorpholine; 5- thiomorpholine; 6- thiomorpholine); 1,2-oxathiolane (3-(1,2-oxathiolane); 4-(1,2-oxathiolane); 5-(1,2-oxathiolane); 1,3-dioxolane (2-(1,3-dioxolane); 4-(1,3-dioxolane); 5-(1,3-dioxolane); tetrahydropyrane; (2-tetrahydropyrane; 3-tetrahydropyrane; 4-tetrahydropyrane; 5-tetrahydropyrane; 6-tetrahydropyrane); hexahydropyridazine (1-(hexahydropyridazine); 2-(hexahydropyridazine); 3-(hexahydropyridazine); 4-(hexahydropyridazine); 5-(hexahydropyridazine); 6-(hexahydropyridazine)), [1,3,2]dioxaborolane, [1,3,6,2]dioxazaborocane

The term "aryl" as used herein includes carbocyclic aromatic ring systems of 5-7 carbon atoms. Aryl is also intended to include the partially hydrogenated derivatives of the carbocyclic systems as well as up to four fused fused aromatic- or partially hydrogenated rings, each ring comprising 5-7 carbon atoms.

The term "heteroaryl" as used herein includes heterocyclic unsaturated ring systems containing, in addition to 2-18 carbon atoms, one or more heteroatoms selected from nitrogen, oxygen and sulphur such as furyl, thienyl, pyrrolyl, heteroaryl is also intended to include the partially hydrogenated derivatives of the heterocyclic systems enumerated below.

The terms "aryl" and "heteroaryl" as used herein refers to an aryl which can be optionally substituted or a heteroaryl which can be optionally substituted and includes phenyl, biphenyl, indenyl, naphthyl (1-naphthyl, 2-naphthyl), N-hydroxytetrazolyl, N-hydroxytriazolyl, N-hydroxyimidazolyl, anthracenyl (1-anthracenyl, 2-anthracenyl, 3-anthracenyl), thiophenyl (2-thienyl, 3-thienyl), furyl (2-furyl, 3-furyl), indolyl, oxadiazolyl, isoxazolyl, quinazolinyl, fluorenyl, xanthenyl, isoindanyl, benzhydryl, acridinyl, thiazolyl, pyrrolyl (2-pyrrolyl), pyrazolyl (3-pyrazolyl), imidazolyl (1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl), triazolyl (1,2,3-triazol-1-yl, 1,2,3-triazol-2-yl 1,2,3-triazol-4-yl, 1,2,4-triazol-3-yl), oxazolyl (2-oxazolyl, 4-oxazolyl, 5-oxazolyl), thiazolyl (2-thiazolyl, 4-thiazolyl, 5-thiazolyl), pyridyl (2-pyridyl, 3-pyridyl, 4-pyridyl), pyrimidinyl (2-pyrimidinyl, 4-

pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl), pyrazinyl, pyridazinyl (3- pyridazinyl, 4-pyridazinyl, 5-pyridazinyl), quinolyl (2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 6-quinolyl, 7-quinolyl, 8-quinolyl), isoquinolyl (1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 5-isoquinolyl, 6-isoquinolyl, 7-isoquinolyl, 8-isoquinolyl), benzo[b]furanyl (2-benzo[b]furanyl, 3-benzo[b]furanyl, 4-benzo[b]furanyl, 5-benzo[b]furanyl, 6-benzo[b]furanyl, 7-benzo[b]furanyl), 2,3-dihydro-benzo[b]furanyl (2-(2,3-dihydro-benzo[b]furanyl), 3-(2,3-dihydro-benzo[b]furanyl), 4-(2,3-dihydro-benzo[b]furanyl), 5-(2,3-dihydro-benzo[b]furanyl), 6-(2,3-dihydro-benzo[b]furanyl), 7-(2,3-dihydro-benzo[b]furanyl), benzo[b]thiophenyl (2-benzo[b]thiophenyl, 3-benzo[b]thiophenyl, 4-benzo[b]thiophenyl, 5-benzo[b]thiophenyl, 6-benzo[b]thiophenyl, 7-benzo[b]thiophenyl), 2,3-dihydro-benzo[b]thiophenyl (2-(2,3-dihydro-benzo[b]thiophenyl), 3-(2,3-dihydro-benzo[b]thiophenyl), 4-(2,3-dihydro-benzo[b]thiophenyl), 5-(2,3-dihydro-benzo[b]thiophenyl), 6-(2,3-dihydro-benzo[b]thiophenyl), 7-(2,3-dihydro-benzo[b]thiophenyl), indolyl (1-indolyl, 2-indolyl, 3-indolyl, 4-indolyl, 5-indolyl, 6-indolyl, 7-indolyl), indazole (1-indazolyl, 3-indazolyl, 4-indazolyl, 5-indazolyl, 6-indazolyl, 7-indazolyl), benzimidazolyl (1-benzimidazolyl, 2-benzimidazolyl, 4-benzimidazolyl, 5-benzimidazolyl, 6-benzimidazolyl, 7-benzimidazolyl, 8-benzimidazolyl), benzoxazolyl (1-benzoxazolyl, 2-benzoxazolyl), benzothiazolyl (1-benzothiazolyl, 2-benzothiazolyl, 4-benzothiazolyl, 5-benzothiazolyl, 6-benzothiazolyl, 7-benzothiazolyl), carbazolyl (1-carbazolyl, 2-carbazolyl, 3-carbazolyl, 4-carbazolyl), 5H-dibenz[b,f]azepine (5H-dibenz[b,f]azepin-1-yl, 5H-dibenz[b,f]azepine-2-yl, 5H-dibenz[b,f]azepine-3-yl, 5H-dibenz[b,f]azepine-4-yl, 5H-dibenz[b,f]azepine-5-yl), 10,11-dihydro-5H-dibenz[b,f]azepine (10,11-dihydro-5H-dibenz[b,f]azepine-1-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-2-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-3-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-4-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-5-yl).

The term "halogen" designates an atom selected from the group consisting of –F, -Cl, -Br and –I.

In the following description of the invention the direction of connections between the various components of a building block should be read left to right. For example an S-C-connecting group –C(=O)-NH- is connected to a Spacer through the carbon atom on the left and to a Carrier through the nitrogen atom on the right hand side.

The Functional Entity carries elements used to interact with host molecules and optionally reactive elements allowing further elaboration of an encoded molecule of a library. Interaction with host molecules like enzymes, receptors and polymers is typically mediated through van der waal's interactions, polar- and ionic interactions and pi-stacking effects. Substituents mediating said effects may be masked by methods known to an individual skilled in the art (Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; 3rd ed.; John Wiley & Sons: New York, 1999.) to avoid undesired interactions or reactions during the preparation of the individual building blocks and during library synthesis. Analogously, reactive elements may be masked by suitably selected protection groups. It is appreciated by one skilled in the art that by suitable protection, a functional entity may carry a wide range of substitutents.

The Functional Entity Precursor may be a masked Functional Entity that is incorporated into an encoded molecule. After incorporation, reactive elements of the Functional Entity may be revealed by un-masking allowing further synthetic operations. Finally, elements mediating recognition of host molecules may be un-masked.

In a certain aspect of the invention the **Functional entity precursor** is of the general formula C(H)(V)-W; in which V is H, -F, -Cl, -Br, -I, -CN, $-NO_2$ or $-OR^{14}$, or selected among the group consisting of C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_4-C_8 alkadienyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, aryl, heteroaryl, -O-aryl and –O-heteroaryl said group being substituted with 0-3 R^{11}, 0-3 R^{12} and 0-3 R^{15};
or V is C_1-C_3 alkylene-$NR^{11}{}_2$, C_1-C_3 alkylene-$NR^{11}C(O)R^{14}$, C_1-C_3 alkylene-$NR^{11}C(O)OR^{14}$, C_1-C_2 alkylene-O-$NR^{11}{}_2$, C_1-C_2 alkylene-O-$NR^{11}C(O)R^{14}$, C_1-C_2 alkylene-O-$NR^{11}C(O)OR^{14}$ substituted with 0-3 R^{15};
W is selected among the group consisting of H, aryl, heteroaryl, $C(=O)OR^{11}$, $C(O)R^{11}$, $C(=O)NR^{11}{}_2$, $C(=O)NR^{11}OR^{11}$, $C(=NR^{11})OR^{11}$, $C(=NOR^{11})$ R^{11}, $C(=NNR^{11}{}_2)R^{11}$, $S(O)R^{11}$, $S(O)_2R^{11}$, $S(O)NR^{11}{}_2$, $S(O)_2NR^{11}{}_2$, -CN, $P(O)$ $R^{11}{}_2$, $-NO_2$, $NR^{11}{}_3{}^+$ or $SR^{11}{}_2{}^+$

Where each individual R^{11} is H or selected independently among the group consisting of C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, aryl, heteroaryl, said group being substituted with 0-3 R^{12} and 0-3 R^{15} and

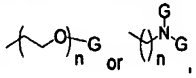
Each individual R^{12} is selected independently from $-N_3$, -CNO, $-C(NOH)NH_2$, -NHOH, $-NHR^4NHR^4$, $-C(O)R^4$, $-SnR^4{}_3$, $-B(OR^4)_2$, $-P(O)(OR^4)_2$ or the group consist-

ing of C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_4-C_8 alkadienyl said group being substituted with 0-2 R^{13},

where R^{13} is independently selected from $-NO_2$, $-C(O)OR^{14}$, $-C(O)R^{14}$, -CN, $-OSiR^{14}_3$, $-OR^{14}$ and $-NR^{14}_2$.

Each individual R^{14} is independently chosen from a group comprising H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, aryl or C_1-C_6 alkylene-aryl substituted with 0-3 substituents independently selected from –F, -Cl, $-NO_2$, $-R^4$, $-OR^4$, $-SiR^4_3$

R^{15} is =O, -F, -Cl, -Br, -I, -CN, $-NO_2$, $-OR^{14}$, $-NR^{14}_2$, $-NR^{14}$-$C(O)R^{14}$, $-NR^{14}$-$C(O)OR^{14}$, $-SR^{14}$, $-S(O)\ R^{14}$, $-S(O)_2R^{14}$, $-COOR^{14}$, $-C(O)NR^{14}_2$ and $-S(O)_2NR^{14}_2$,

R^{16} is selected independently from H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, aryl, C_1-C_6 alkylene-aryl,  or , G is H or C_1-C_6 alkyl and n is 1,2,3 or 4.

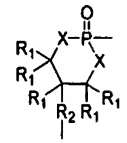
In a preferred embodiment of the present invention, W is selected among the group consisting of $C(=O)OR^{11}$, $C(O)R^{11}$, $C(=O)NR^{11}_2$, $S(O)_2R^{11}$, $S(O)_2NR^{11}_2$, or –CN

In yet a preferred embodiment of the present invention, V is C_1-C_6 alkyl, aryl or heteroaryl said group being substituted with 0-3 R^{11}, 0-3 R^{12} and 0-3 R^{15} or V is C_1-C_3 alkylene-$NR^{11}C(O)R^{14}$ or C_1-C_3 alkyl-ene-$NR^{11}C(O)OR^{14}$ substituted with 0-3 R^{15};

In yet a preferred embodiment of the present invention, R^{11} is H or selected independently among the group consisting of C_1-C_6 alkyl, C_3-C_7 cycloalkyl, aryl, or heteroaryl, said group being substituted with 0-3 R^{12} and 0-3 R^{15} .

The function of the carrier is to ensure a high reactivity of the functional entity precursor towards a broad range of carbonyl recipient reactive groups. Substituents on the carrier alter the reactivity of the functional group precursor and can be designed to direct the stereochemically outcome of the reaction by an individual skilled in the art by evaluation of initial attempts. The transferability and the stereoselectivity may be adjusted in response to the chemical composition of the functional entity precursor, to the nature of the complementing element, to the conditions under which the transfer and recognition is performed, etc.

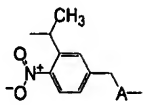
In a preferred embodiment, the carrier is:



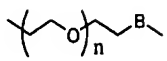
wherein R^2 is a valence bond or arylene.

The S-C-connecting group provide a means for connecting the Spacer and the Carrier. As such it is primarily of synthetic convenience and does not influence the function of a building block. In a preferred embodiment of the present invention, the S-C connecting group is -S-S-, -C_1-C_6 alkylene-S-S -, -C(=O)-NH-(C_1-C_6 alkylene)-, -C(=O)-, or -C(=O)-Arylene-$C(R^{16})_2$-NR^{16}-C(=O)-

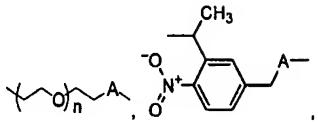
The spacer serves to distance the functional entity precursor to be transferred from the bulky complementing element. Thus, when present, the identity of the spacer is not crucial for the function of the building block. It may be desired to have a spacer which can be cleaved by light. In this occasion, the spacer is provided with e.g. the group



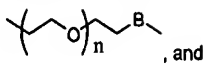
In the event an increased hydrophilicity is desired the spacer may be provided with a polyethylene glycol part of the general formula:



In a certain aspect of the invention the **Spacer** is -A-, a group C_1-C_6 alkylene-A-, C_2-C_6 alkenylene-A-, or C_2-C_6 alkynylene-A- optionally substituted with 1 to 3 hydroxy groups, or



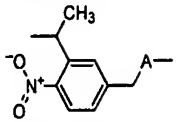
said spacer being connected through A to a moiety selected from

-B-, —$(CH_2)_n$—B—,  , and

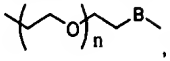
—$(CH_2)_n$—S—S—$(CH_2)_m$—B—

where A is a valence bond, -NR^{16}-, –C(O)NR^{16}-, - NR^{16}-C(O)-, -O-, -S-, -C(O)-O- or –OP(=O)(O^-)-O-; B is a valence bond, -O-, -S-, –NR^{16}-, -C(O)- or –C(O)NR^{16}- and connects to S-C-connecting group; and n and m independently are integers ranging from 1 to 10.

In a preferred embodiment the **Spacer** is a valence bond, C_1-C_6 alkylene-A-, C_2-C_6 alkenylene-A-, C_2-C_6 alkynylene-A-, or



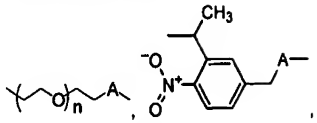
said spacer optionally being connected through A to a moiety selected from

—$(CH_2)_n$—B—,  , and

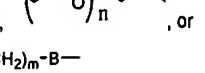
—$(CH_2)_n$—S—S—$(CH_2)_m$—B—

where A is a valence bond, –C(O)NR^{16}-, -NR^{16}- , -O-, -S-, or -C(O)-O-; B is a valence bond, -O-, -S-, –NR^{16}- or –C(O)NR^{16}- and connects to S-C-connecting group; R^{16} is selected independently from H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, aryl or C_1-C_6 alkylene-aryl and n and m independently are integers ranging from 1 to 10.

In a more preferred aspect of the invention the **spacer** is -A-, C_1-C_6 alkylene-A-, C_2-C_6 alkenylene-A,

 ,

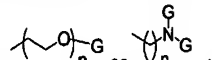
said spacer being connected through A to a moiety selected from

-B-, —$(CH_2)_n$—B—,  , or

—$(CH_2)_n$—S—S—$(CH_2)_m$—B—

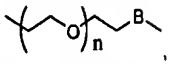
where A is a valence bond, -NR^{16}-, –C(O)NR^{16}-, -NR^{16}-C(O)-, -O-, -S-, -C(O)-O-, or –OP(=O)(O^-)-O-; B is a valence bond, -S-, –NR^{16}-, or -C(O)- and connects to S-C-connecting group;

n and m independently are integers ranging from 1 to 10 and

R^{16} is selected independently from H,  or , wherein G is H or C_1-C_6 alkyl.

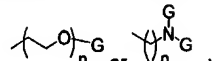
Still more preferred the **spacer** is C_2-C_6 alkenylene-A,

said spacer being connected through A to a moiety selected from

-B-, or —$(CH_2)_n$—B—,  ,

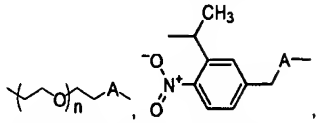
where A is a valence bond, –C(O)NR^{16}-, -NR^{16}-C(O)-, -S-, -C(O)-O- or –OP(=O)(O^-)-O-; B is a valence bond, -S-, –NR^{16}-, or -C(O)- and connects to S-C-connecting group;

n and m independently are integers ranging from 1 to 10 and

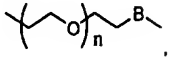
R^{16} is selected independently from H,  or , wherein G is H or C_1-C_6 alkyl; and the spacer is connected to the complementing element through a nucleobase.

The spacer may be attached to the complementing element in any appropriate way. Though it is preferred that the spacer is attached to the 5-position of a pyrimidine type nucleobase or the 7-position of a purine or 7-deaza-purine type nucleobase.

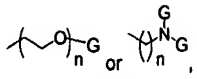
In aspect of the invention it is preferred that the complementing element is connected to the spacer via a phosphorus group. It is then preferred that **spacer** is -A-,

 ,

said spacer being connected through A to a moiety selected from

-B-, or —$(CH_2)_n$—B—,  ,

where A is a valence bond, -NR^{18}-C(O)-, -O-, or -S-; B is a valence bond, -S-, -NR^{18}-, or -C(O)- and connects to S-C-connecting group;
n and m independently are integers ranging from 1 to 10 and

R^{18} is selected independently from H,  wherein G is H or C_1-C_6 alkyl; and the spacer is connected to the complementing element via a phosphorus group.

The phosphorus group may be a phosphate or a thiophosphate group attached to a 3' or a 5' end of a complementing element.

In a preferred embodiment, the complementing element serves the function of recognising a coding element. The recognition implies that the two parts are capable of interacting in order to assemble a complementing element – coding element complex. In the biotechnological field a variety of interacting molecular parts are known which can be used according to the invention. Examples include, but are not restricted to protein-protein interactions, protein-polysaccharide interactions, RNA-protein interactions, DNA-DNA interactions, DNA-RNA interactions, RNA-RNA interactions, biotin-streptavidin interactions, enzyme-ligand interactions, antibody-ligand interaction, protein-ligand interaction, ect.

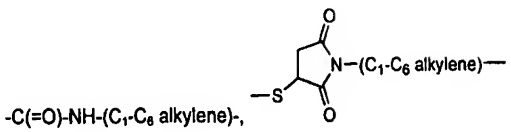
The interaction between the complementing element and coding element may result in a strong or a weak bonding. If a covalent bond is formed between the parties of the affinity pair the binding between the parts can be regarded as strong, whereas the establishment of hydrogen bondings, interactions between hydrophobic domains, and metal chelation in general results in weaker bonding. In general relatively weak bonding is preferred. In a preferred aspect of the invention, the complementing element is capable of reversible interacting with the coding element so as to provide for an attachment or detachment of the parts in accordance with the changing conditions of the media.

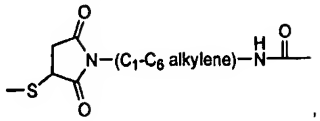
In a preferred aspect of the invention, the interaction is based on nucleotides, i.e. the complementing element is a nucleic acid. Preferably, the complementing element is a sequence of nucleotides and the coding element is a sequence of nucleotides capable of hybridising to the complementing element. The sequence of nucleotides carries a series of nucleobases on a backbone. The nucleobases may be any chemical entity able to be specifically recognized by a complementing entity. The nucleobases are usually selected from the natural nucleobases (adenine, guanine, uracil, thymine, and cytosine) but also the other nucleobases obeying the Watson-Crick hydrogen-bonding rules may be used, such as the synthetic nucleobases disclosed in US 6,037,120. Examples of natural and non-natural nucleobases able to perform a specific pairing are shown in figure 2. The backbone of the sequence of nucleotides may be any backbone able to aggregate the nucleobases is a sequence. Examples of backbones are shown in figure 4. In some aspects of the invention the addition of non-specific nucleobases to the complementing element is advantegeous, figure 3

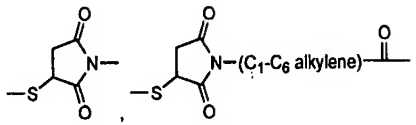
The coding element can be an oligonucleotide having nucleobases which complements and is specifically recognised by the complementing element, i.e. in the event the complementing element contains cytosine, the coding element part contains guanine and visa versa, and in the event the complementing element contains thymine or uracil the coding element contains adenine.

The complementing element may be a single nucleobase. In the generation of a library, this will allow for the incorporation of four different functional entities into the template-directed molecule. However, to obtain a higher diversity a complementing element preferably comprises at least two and more preferred at least three nucleotides. Theoretically, this will provide for 4^2 and 4^3, respectively, different functional entities uniquely identified by the complementing element. The complementing element will usually not comprise more than 100 nucleotides. It is preferred to have complementing elements with a sequence of 3 to 30 nucleotides.

The part of the linker connecting the spacer with the carrier is denoted Spacer-Carrier-Connecting group or S-C-connecting group for short. The connecting group is a convenient chemical means and may be designed not to have adverse affect on the ability of the building block to transfer the functional entity precursor. In a certain aspect of the invention the **S-C-connecting group** is a valence bond, –NH-C(=O)-, –NH-C(=O)-C_1-C_6 alkylene-, -S-S-, -S-S-C_1-C_6 alkylene-, -C_1-C_6 alkylene-S-S -,

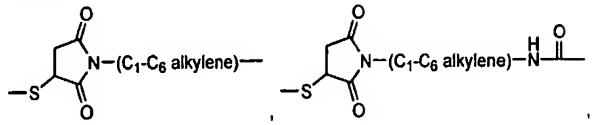






-NH-C(=O)-Arylene-C(R^{16})$_2$-NH-C(=O)-, -C(=O)-, -C(=O)-C_1-C_6 alkylene- or -C(=O)-Arylene-C(R^{16})$_2$-NR^{16}-C(=O)-, where the right hand side of the formulae connects to the carrier.

In another aspect, the **S-C-connecting group** is a valence bond, –NH-C(=O)-, –NH-C(=O)-C_1-C_6 alkylene-, -S-S-, -S-S-C_1-C_6 alkylene-, -C(=O)-NH-(C_1-C_6 alkylene)-,



-NH-C(=O)-Arylene-C(R^{16})$_2$-NH-C(=O)-, where the right hand side of the formulae connects to the carrier.

In a preferred aspect of the invention the **S-C-connecting group** is -S-S-, -C_1-C_6 alkylene-S-S -, -C(=O)-NH-(C_1-C_6 alkylene)-, -C(=O)-, or -C(=O)-Arylene-C(R^{16})$_2$-NR^{16}-C(=O)-, where the right hand side of the formulae connects to the carrier.

In a still more preferred aspect of the invention the **S-C-connecting group** is -S-S-, -C(=O)-, or -C(=O)-Arylene-C(R^{16})$_2$-NR^{16}-C(=O)-, where the right hand side of the formulae connects to the carrier.

The building blocks of the present invention can be used in a method for transferring a functional entity precursor to a recipient reactive group, said method comprising the steps of

providing one or more building blocks as described above and

contacting the one or more building blocks with a corresponding encoding element associated with a recipient reactive group under conditions which allow for a recognition between the one or more complementing elements and the encoding elements, said contacting being performed prior to, simultaneously with, or subsequent to a transfer of the functional entity precursor to the recipient reactive group.

The encoding element may comprise one, two, three or more codons, i.e. sequences that may be specifically recognised by a complementing element. Each of the codons may be separated by a suitable spacer group. Preferably, all or at least a majority of the codons of the template are arranged in sequence and each of the codons are separated from a neighbouring codon by a spacer group. Generally, it is preferred to have more than two codons on the template to allow for the synthesis of more complex encoded molecules. In a preferred aspect of the invention the number of codons of the encoding element is 2 to 100. Still more preferred are encoding elements comprising 3 to 10 codons. In another aspect, a codon comprises 1 to 50 nucleotides and the complementing element comprises a sequence of nucleotides complementary to one or more of the encoding sequences.

The recipient reactive group may be associated with the encoding element in any appropriate way. Thus, the reactive group may be associated covalently or non-covalently to the encoding element. In one embodiment the recipient reactive group is linked covalently to the encoding element through a suitable linker which may be separately cleavable to release the reaction product. In another embodiment, the reactive group is coupled to a complementing element, which is capable of recognising a sequence of nucleotides on the encoding element, whereby the recipient reactive group becomes attached to the encoding element by hybridisation. Also, the recipient reactive group may be part of a chemical scaffold, i.e. a chemical entity having one or more reactive groups available for receiving a functional entity precursor from a building block.

The recipient reactive group may be any group able to cleave the Carrier-Funtional Entity Precursor bond to release the functional entity precursor. The recipient reactive group is electrophilic, such as an aldehyde or a ketone. The electrophile usually reacts with an anion formed on the functional entity precursor. The outcome of the

reaction is a transformation of the C=(O) recipient reactive group into a C=(Functional entity precursor) moiety.

According to a preferred aspect of the invention the building blocks are used for the formation of a library of compounds. The complementing element of the building block is used to identify the functional entity. Due to the enhanced proximity between reactive groups when the complementing entity and the encoding element are contacted, the functional entity precursor together with the identity programmed in the complementing element is transferred to the encoding element associated with recipient reactive group. Thus, it is preferred that the sequence of the complementing element is unique in the sense that the same sequence is not used for another functional entity. The unique identification of the functional entity enable the possibility of decoding the encoding element in order to determine the synthetic history of the molecule formed. In the event two or more functional entities have been transferred to a scaffold, not only the identity of the transferred functional entities can be determined. Also the sequence of reaction and the type of reaction involved can be determined by decoding the encoding element. Thus, according to a preferred embodiment of the invention, each different member of a library comprises a complementing element having a unique sequence of nucleotides, which identifies the functional entity.

Brief description of the drawings

Figure 1. Two setups for Functional Entity Precursor Transfer
Figure 2. Examples of specific base pairing
Figure 3. Example of non-specific base-pairing
Figure 4. Backbone examples
Figure 5 Three examples of building blocks

Detailed Description of the Invention

A building block of the present invention is characterized by its ability to transfer its functional entity precursor to a recipient reactive group. This is done by transforming the C=O double bond of a scaffold to a C=(Functional entity precursor) moiety.

Two setups for generalized functional entity precursor transfer from a building block are depicted in figure 1. In the first example, one complementing element of a building block recognizes a coding element carrying another functional entity precursor, hence bringing the functional entities in close proximity. This results in a reaction between functional entity precursor 1 and 2 forming a covalent bond between these concurrent with the cleavage of the bond between functional entity precursor 2 and its carrier. In the second example, a coding element brings together two building blocks resulting in functional entity precursor transfer from one building block to the other.

In library generation of chemical entities the tolerance towards a broad range of building blocks is of outmost importance. Useful building blocks for generation of libraries used for drug discovery should therefore posses the necessary reactivity to enable the transfer of the functional entity precursor to a broad range of reaction counter parts, resulting in generation of a highly diverse library, and not only a limited number of products. The Wittig reaction is a powerful C=C bond forming reaction, but the number of useful building blocks are limited to primarily aldehydes. Therefore, the present invention particularly relates to demonstrate the broadness of building blocks capable of acting as C=C bond forming reagents in a modified Wittig reaction (HWE reaction), which allow reaction with aldehydes as well as ketones. Furthermore, use of HWE-building blocks opens up the possibility of directing the stereochemically outcome of the reaction by carefully selecting the substituents on the carrier of the building block.

Figure 5 illustrates three specific compounds according to the invention. For illustrative purposes the individual features used in the claims are indicated. The upper compound is an example of a building block wherein the linker is backbone attached at the 3'-position. The first part of the linker, i.e. the spacer, is an aliphatic chain ending in a nitrogen atom. The nitrogen atom bridges to the S-C-connecting group, which is an N-acylated arylmethyleamine. The carrier attached to the left hand side carbonyl group of the S-C-connecting group is a six-membered phosphinane structure. The phosphor atom is attached to the functional entity precursor, which is an aliphatic ester. When the building block is presented to a recipient reactive group, such as aldehyde or a ketone, the aliphatic ester is transferred forming the C=C double bond of an $\alpha - \beta$ unsaturated ester.

The middle compound illustrates a 5' attachment of a linker. The linker is linked through a phosphate group and extends into a three membered aliphatic chain.

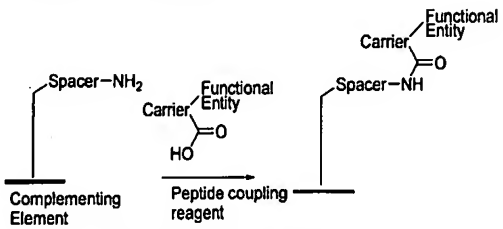
Through another phosphate group and a PEG linker the complementing element is linked via an amide bond to the Carrier. When the building block is presented to a ketone or an aldehyde the functional entity precursor is transferred forming an α – β unsaturated ester.

The lower compound illustrates a nucleobase attachment of the linker. The linker attaches to the 5 position of a pyrimidine type nucleobase and extents through an α – β unsaturated N-methylated amide to the S-C-connecting group, which is a 4-amino methyl benzoic acid derivative. The functional entity precursor can be transferred to a recipient reactive group forming an α – β unsaturated keton carrying a protected amine group.

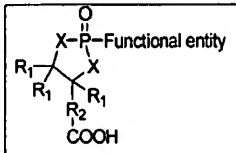
Assembly of building blocks

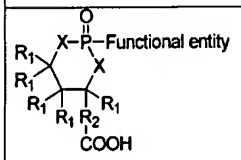
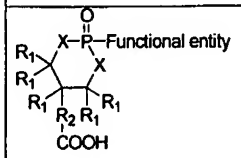
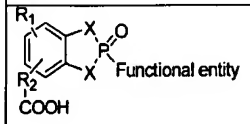
The Carrier-Functional Entity Precursor ensemble may be bound to the Spacer by several different reactions.

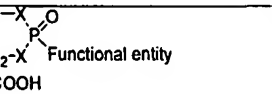
Formation of an amide bond between a carboxylic acid of the Carrier and an amine group of a Spacer



Examples of Carrier-Functional entity reagents:

	X = NR,O, S, Se; where each of the individual X is chosen independently R = H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, aryl or heteroaryl R1 = H, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl C_2-C_6 alkenyl, C_2-C_6 alkynyl or aryl; where each of the R1 groups are chosen independently R2 = a valence bond, C_1-C_6 Alkylene, C_2-C_6 Alkenylene, C_2-C_6 Alkynylene, Arylene, Heteroarylene, C_1-C_6 Alkylene-arylene or C_1-C_6 Alkylene-heteroarylene

	roarylene, C_1-C_6 Alkylene-arylene or C_1-C_6 Alkylene-heteroarylene
	X = NR,O, S, Se; where each of the individual X is chosen independently R = H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, aryl or heteroaryl R1 = H, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl C_2-C_6 alkenyl, C_2-C_6 alkynyl or aryl, where each of the R1 groups are chosen independently R2 = a valence bond, C_1-C_6 Alkylene, C_2-C_6 Alkenylene, C_2-C_6 Alkynylene, Arylene, Heteroarylene, C_1-C_6 Alkylene-arylene or C_1-C_6 Alkylene-heteroarylene
	X = NR,O, S, Se; where each of the individual X is chosen independently R = H, C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, aryl or heteroaryl R1 = H, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl C_2-C_6 alkenyl, C_2-C_6 alkynyl or aryl; where each of the R1 groups are chosen independently R2 = a valence bond, C_1-C_6 Alkylene, C_2-C_6 Alkenylene, C_2-C_6 Alkynylene, Arylene, Heteroarylene, C_1-C_6 Alkylene-arylene or C_1-C_6 Alkylene-heteroarylene
	X = NR,O, S, Se; where each of the individual X is chosen independently R = H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, aryl or heteroaryl R1 = H, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl C_2-C_6 alkenyl, C_2-C_6 alkynyl, aryl, Halogen, NO_2, CN, $C(Halogen)_3$, C(O)R'', C(O)NHR'', $C(O)NR''_2$, -NC(O)R'', $S(O)_2NHR''$, $S(O)_2NR''_2$, $S(O)_2R''$, $-P(O)_2$-R'', P(O)-R'', S(O)-R'', P(O)-OR'', S(O)-OR'', $-N^+R''_3$ R2 = a valence bond, C_1-C_6 Alkylene, C_1-C_6

	Alkenylene, C_1-C_6 Alkynylene, Arylene, Heteroarylene, C_1-C_6 Alkylene-arylene or C_1-C_6 Alkylene-heteroarylene
 Functional entity	X = NR,O, S, Se; where each of the individual X is chosen independently R = H, C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, aryl or heteroaryl R1 = H, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl C_2-C_6 alkenyl, C_2-C_6 alkynyl, aryl, heteroaryl, or a combination thereof R2 = a valence bond, C_1-C_6 Alkylene, C_1-C_6 Alkenylene, C_1-C_6 Alkynylene, Arylene, Heteroarylene, C_1-C_3 Alkylene substituted with 1-7 halogens selected from the group consisting of –F, -Cl or -Br, C_1-C_6 Alkylene-arylene or C_1-C_6 Alkylene-heteroarylene

According to the invention, the functional entity precursor is of the formula C(H)(V)-W. In an aspect of the invention V is independently H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_4-C_8 alkadienyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, aryl or heteroaryl, optionally substituted with one or more substituents selected from the group consisting of SnR^5R^6,R^7, $Sn(OR^5)R^6R^7$, $Sn(OR^5)(OR^6)R^7$, BR^5R^6, $B(OR^5)R^6$, $B(OR^5)(OR^6)$, halogen, CN, CNO, $C(halogen)_3$, =O, $=NOR^5$, $=NNR^5R^6$, OR^5, $OC(=O)R^5$, $OC(=O)OR^5$, $OC(=O)NR^5R^6$, SR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$, NO_2, N_3, NR^5R^6, $N^+R^5R^6R^7$, NR^5OR^6, $NR^5NR^6R^7$, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, NC, $P(=O)(OR^5)OR^6$, $P^+R^5R^6R^7$, $C(=O)R^5$, $C(=NR^5)R^6$, $C(=NOR^5)R^6$, $C(=NNR^5R^6)$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$, $C(=O)NR^5NR^6R^7$, $C(=NR^5)NR^6R^7$, $C(=NOR^5)NR^6R^7$ or R^8,

W is selected among the group consisting of H, aryl, heteroaryl, $C(=O)OR^5$, $C(O)R^5$, $C(=O)NR^5_2$, $C(=O)NR^5OR^6$, $C(=NR^5)OR^6$, $C(=NOR^5)$ R^6, $C(=NNR^5_2)R^6$, $S(O)R^5$, $S(O)_2R^5$, $S(O)NR^5_2$, $S(O)_2NR^5_2$, -CN, $P(O)R^5_2$, $-NO_2$, $NR^5_3{}^+$ or $SR^5_2{}^+$

wherein,

R^5, R^6, R^7 and R^8 independently is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_4-C_8 alkadienyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, aryl or heteroaryl and wherein R^5 and R^6 may together form a 3-8 membered heterocyclic ring or R^5 and R^7 may together form a 3-8 membered heterocyclic ring or R^6 and R^7 may together form a 3-8 membered heterocyclic ring,

In another preferred embodiment,

V independently is H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, aryl or heteroaryl, optionally substituted with one or more substituents selected from the group consisting of halogen, CN, $C(halogen)_3$, =O, $=NOR^5$, $=NNR^5R^6$, OR^5, $OC(=O)R^5$, $OC(=O)OR^5$, $OC(=O)NR^5R^6$, SR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$, NO_2, NR^5R^6, NR^5OR^6, $NR^5NR^6R^7$, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, $P(=O)(OR^5)OR^6$, $C(=O)R^5$, $C(=NR^5)R^6$, $C(=NOR^5)R^6$, $C(=NNR^5R^6)$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$, $C(=O)NR^5NR^6R^7$, $C(=NR^5)NR^6R^7$, $C(=NOR^5)NR^6R^7$ or R^8,

wherein,

R^5, R^6, R^7 and R^8 independently is H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, aryl or heteroaryl and wherein R^5 and R^6 may together form a 3-8 membered heterocyclic ring or R^5 and R^7 may together form a 3-8 membered heterocyclic ring or R^6 and R^7 may together form a 3-8 membered heterocyclic ring,

In still another preferred embodiment,

V independently is H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, aryl or heteroaryl, optionally substituted with one or more substituents selected from the group consisting of F, Cl, CN, CF_3, =O, $=NOR^5$, $=NNR^5R^6$, OR^5, $OC(=O)R^5$, $OC(=O)OR^5$, $OC(=O)NR^5R^6$, SR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$, NO_2, NR^5R^6, NR^5OR^6, $NR^5NR^6R^7$, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, $P(=O)(OR^5)OR^6$, $C(=O)R^5$, $C(=NR^5)R^6$, $C(=NOR^5)R^6$, $C(=NNR^5R^6)$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$, $C(=O)NR^5NR^6R^7$, $C(=NR^5)NR^6R^7$, $C(=NOR^5)NR^6R^7$ or R^8,

wherein,

R^5, R^6, R^7 and R^8 independently is H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, aryl or heteroaryl and wherein R^5 and R^6 may together form a 3-8 membered heterocyclic ring or R^5 and R^7 may together form a 3-8 membered heterocyclic ring or R^6 and R^7 may together form a 3-8 membered heterocyclic ring,

In still another preferred embodiment,

V independently is H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, aryl or heteroaryl, optionally substituted with one or more substituents selected from the group consisting of F, Cl, CN, CF_3, =O, $=NOR^5$, $=NNR^5R^6$, OR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$, NO_2, NR^5R^6, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, $C(=O)R^5$, $C(=NOR^5)R^6$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$ or R^8, wherein,

R^5, R^6, R^7 and R^8 independently is H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, aryl or heteroaryl and wherein R^5 and R^6 may together form a 3-8 membered heterocyclic ring or R^5 and R^7 may together form a 3-8 membered heterocyclic ring or R^6 and R^7 may together form a 3-8 membered heterocyclic ring,

In still another preferred embodiment,

V independently is H, methyl, ethyl, propyl, butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, phenyl, naphtyl, thienyl, furyl, pyridyl, quinolinyl or isoquinolinyl optionally substituted with one or more substituents selected from the group consisting of F, Cl, CN, CF_3, =O, $=NOR^5$, $=NNR^5R^6$, OR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$, NO_2, NR^5R^6, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, $C(=O)R^5$, $C(=NOR^5)R^6$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$ or R^8, wherein,

R^5, R^6, R^7 and R^8 independently is H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, aryl or heteroaryl and wherein R^5 and R^6 may together form a 3-8 membered heterocyclic ring or R^5 and R^7 may together form a 3-8 membered heterocyclic ring or R^6 and R^7 may together form a 3-8 membered heterocyclic ring,

In still another preferred embodiment,

V independently is H, methyl, ethyl, propyl, butyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl optionally substituted with one or more substituents selected from the group consisting of F, Cl, CN, CF_3, =O, $=NOR^5$, $=NNR^5R^6$, OR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$, NO_2, NR^5R^6, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, $C(=O)R^5$, $C(=NOR^5)R^6$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$ or R^8, wherein,

R^5, R^6, R^7 and R^8 independently is H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, aryl or heteroaryl and wherein R^5 and R^6 may together form a 3-8 membered heterocyclic ring or R^5 and R^7 may together form a 3-8 membered heterocyclic ring or R^6 and R^7 may together form a 3-8 membered heterocyclic ring,

In still another preferred embodiment,

V independently is H, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl or morpholinyl optionally substituted with one or more substituents selected from the group consisting of F, Cl, CN, CF_3, =O, $=NOR^5$, $=NNR^5R^6$, OR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$, NO_2, NR^5R^6, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, $C(=O)R^5$, $C(=NOR^5)R^6$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$ or R^8, wherein,

R^5, R^6, R^7 and R^8 independently is H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, aryl or heteroaryl and wherein R^5 and R^6 may together form a 3-8 membered heterocyclic ring or R^5 and R^7 may together form a 3-8 membered heterocyclic ring or R^6 and R^7 may together form a 3-8 membered heterocyclic ring,

In still another preferred embodiment,

V independently is H, phenyl, naphtyl, thienyl, furyl, pyridyl, quinolinyl or isoquinolinyl optionally substituted with one or more substituents selected from the group consisting of F, Cl, CN, CF_3, =O, $=NOR^5$, $=NNR^5R^6$, OR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$, NO_2, NR^5R^6, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, $C(=O)R^5$, $C(=NOR^5)R^6$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$ or R^8, wherein,

R^5, R^6, R^7 and R^8 independently is H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, aryl or heteroaryl and wherein R^5 and R^6 may together form a 3-8 membered heterocyclic ring or R^5 and R^7 may together form a 3-8 membered heterocyclic ring or R^6 and R^7 may together form a 3-8 membered heterocyclic ring,

In still another preferred embodiment,

V independently is H, phenyl or naphtyl optionally substituted with one or more substituents selected from the group consisting of F, Cl, CN, CF_3, =O, $=NOR^5$, $=NNR^5R^6$, OR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$, NO_2, NR^5R^6, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, $C(=O)R^5$, $C(=NOR^5)R^6$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$ or R^8, wherein,

R^5, R^6, R^7 and R^8 independently is H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, aryl or heteroaryl and wherein R^5 and R^6 may together form a 3-8 membered heterocyclic ring or R^5 and R^7 may together form a 3-8 membered heterocyclic ring or R^6 and R^7 may together form a 3-8 membered heterocyclic ring,

In still another preferred embodiment,
V independently is H, thienyl, furyl, pyridyl, quinolinyl or isoquinolinyl optionally substituted with one or more substituents selected from the group consisting of F, Cl, CN, CF_3, =O, $=NOR^5$, $=NNR^5R^6$, OR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$, NO_2, NR^5R^6, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, $C(=O)R^5$, $C(=NOR^5)R^6$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$ or R^8,
wherein,
R^5, R^6, R^7 and R^8 independently is H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, aryl or heteroaryl and wherein R^5 and R^6 may together form a 3-8 membered heterocyclic ring or R^5 and R^7 may together form a 3-8 membered heterocyclic ring or R^6 and R^7 may together form a 3-8 membered heterocyclic ring,

In still another preferred embodiment,
V independently is H, methyl, ethyl, propyl, butyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl optionally substituted with one or more substituents selected from the group consisting of F, Cl, CN, CF_3, =O, $=NOR^5$, $=NNR^5R^6$, OR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$, NO_2, NR^5R^6, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, $C(=O)R^5$, $C(=NOR^5)R^6$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$ or R^8,
wherein,
R^5, R^6, R^7 and R^8 independently is H, methyl, ethyl, propyl, butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, naphthyl, thienyl, furyl, pyridinyl, quinolinyl or isoquinolinyl and wherein R^5 and R^6 may together form a 3-8 membered heterocyclic ring or R^5 and R^7 may together form a 3-8 membered heterocyclic ring or R^6 and R^7 may together form a 3-8 membered heterocyclic ring,

In still another preferred embodiment,
V independently is H, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl or morpholinyl optionally substituted with one or more substituents selected from the group consisting of F, Cl, CN, CF_3, =O, $=NOR^5$, $=NNR^5R^6$, OR^5, $S(=O)R^5$, $S(=O)_2R^5$,

$S(=O)_2NR^5R^6$, NO_2, NR^5R^6, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, $C(=O)R^5$, $C(=NOR^5)R^6$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$ or R^8,
wherein,
R^5, R^6, R^7 and R^8 independently is H, methyl, ethyl, propyl, butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, naphthyl, thienyl, furyl, pyridinyl, quinolinyl or isoquinolinyl and wherein R^5 and R^6 may together form a 3-8 membered heterocyclic ring or R^5 and R^7 may together form a 3-8 membered heterocyclic ring or R^6 and R^7 may together form a 3-8 membered heterocyclic ring,

In still another preferred embodiment,
V independently is H, phenyl, naphtyl, thienyl, furyl, pyridyl, quinolinyl or isoquinolinyl optionally substituted with one or more substituents selected from the group consisting of F, Cl, CN, CF_3, =O, $=NOR^5$, $=NNR^5R^6$, OR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$, NO_2, NR^5R^6, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, $C(=O)R^5$, $C(=NOR^5)R^6$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$ or R^8,
wherein,
R^5, R^6, R^7 and R^8 independently is H, methyl, ethyl, propyl, butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, naphthyl, thienyl, furyl, pyridinyl, quinolinyl or isoquinolinyl and wherein R^5 and R^6 may together form a 3-8 membered heterocyclic ring or R^5 and R^7 may together form a 3-8 membered heterocyclic ring or R^6 and R^7 may together form a 3-8 membered heterocyclic ring,

In still another preferred embodiment,
V independently is H, phenyl or naphtyl optionally substituted with one or more substituents selected from the group consisting of F, Cl, CN, CF_3, =O, $=NOR^5$, $=NNR^5R^6$, OR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$, NO_2, NR^5R^6, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, $C(=O)R^5$, $C(=NOR^5)R^6$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$ or R^8,
wherein,
R^5, R^6, R^7 and R^8 independently is H, methyl, ethyl, propyl, butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, naphthyl, thienyl, furyl, pyridinyl, quinolinyl or isoquinolinyl and wherein R^5 and R^6 may together form a 3-8 membered heterocyclic ring or R^5 and R^7 may together form a 3-8 membered heterocyclic ring or R^6 and R^7 may together form a 3-8 membered heterocyclic ring,

In still another preferred embodiment,
V independently is H, thienyl, furyl, pyridyl, quinolinyl or isoquinolinyl optionally substituted with one or more substituents selected from the group consisting of F, Cl, CN, CF_3, =O, $=NOR^5$, $=NNR^5R^6$, OR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$, NO_2, NR^5R^6, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, $C(=O)R^5$, $C(=NOR^5)R^6$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$ or R^8,
wherein,
R^5, R^6, R^7 and R^8 independently is H, methyl, ethyl, propyl, butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, naphthyl, thienyl, furyl, pyridinyl, quinolinyl or isoquinolinyl and wherein R^5 and R^6 may together form a 3-8 membered heterocyclic ring or R^5 and R^7 may together form a 3-8 membered heterocyclic ring or R^6 and R^7 may together form a 3-8 membered heterocyclic ring,

In still another preferred embodiment,
V independently is H, methyl, ethyl, propyl, butyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl optionally substituted with one or more substituents selected from the group consisting of F, Cl, CN, CF_3, =O, $=NOR^5$, $=NNR^5R^6$, OR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$, NO_2, NR^5R^6, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, $C(=O)R^5$, $C(=NOR^5)R^6$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$ or R^8,
wherein,
R^5, R^6, R^7 and R^8 independently is H, methyl, ethyl, propyl or butyl and wherein R^5 and R^6 may together form a 3-8 membered heterocyclic ring or R^5 and R^7 may together form a 3-8 membered heterocyclic ring or R^6 and R^7 may together form a 3-8 membered heterocyclic ring,

In still another preferred embodiment,
V independently is H, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl or morpholinyl optionally substituted with one or more substituents selected from the group consisting of F, Cl, CN, CF_3, =O, $=NOR^5$, $=NNR^5R^6$, OR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$, NO_2, NR^5R^6, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, $C(=O)R^5$, $C(=NOR^5)R^6$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$ or R^8,
wherein,
R^5, R^6, R^7 and R^8 independently is H, methyl, ethyl, propyl or butyl and wherein R^5 and R^6 may together form a 3-8 membered heterocyclic ring or R^5 and R^7 may together form a 3-8 membered heterocyclic ring or R^6 and R^7 may together form a 3-8 membered heterocyclic ring,

In still another preferred embodiment,
V independently is H, phenyl, naphtyl, thienyl, furyl, pyridyl, quinolinyl or isoquinolinyl optionally substituted with one or more substituents selected from the group consisting of F, Cl, CN, CF_3, =O, $=NOR^5$, $=NNR^5R^6$, OR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$, NO_2, NR^5R^6, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, $C(=O)R^5$, $C(=NOR^5)R^6$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$ or R^8,
wherein,
R^5, R^6, R^7 and R^8 independently is H, methyl, ethyl, propyl or butyl and wherein R^5 and R^6 may together form a 3-8 membered heterocyclic ring or R^5 and R^7 may together form a 3-8 membered heterocyclic ring or R^6 and R^7 may together form a 3-8 membered heterocyclic ring,

In still another preferred embodiment,
V independently is H, phenyl or naphtyl optionally substituted with one or more substituents selected from the group consisting of F, Cl, CN, CF_3, =O, $=NOR^5$, $=NNR^5R^6$, OR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$, NO_2, NR^5R^6, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, $C(=O)R^5$, $C(=NOR^5)R^6$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$ or R^8,
wherein,
R^5, R^6, R^7 and R^8 independently is H, methyl, ethyl, propyl or butyl and wherein R^5 and R^6 may together form a 3-8 membered heterocyclic ring or R^5 and R^7 may together form a 3-8 membered heterocyclic ring or R^6 and R^7 may together form a 3-8 membered heterocyclic ring,

In still another preferred embodiment,
V independently is H, thienyl, furyl, pyridyl, quinolinyl or isoquinolinyl optionally substituted with one or more substituents selected from the group consisting of F, Cl, CN, CF_3, =O, $=NOR^5$, $=NNR^5R^6$, OR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$, NO_2, NR^5R^6, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, $C(=O)R^5$, $C(=NOR^5)R^6$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$ or R^8,
wherein,

R^5, R^6, R^7 and R^8 independently is H, methyl, ethyl, propyl or butyl and wherein R^5 and R^6 may together form a 3-8 membered heterocyclic ring or R^5 and R^7 may together form a 3-8 membered heterocyclic ring or R^6 and R^7 may together form a 3-8 membered heterocyclic ring,

In still another preferred embodiment,
V independently is methyl, ethyl, propyl, butyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl optionally substituted with one or more substituents selected from the group consisting of F, Cl, CN, CF_3, =O, $=NOR^5$, $=NNR^5R^6$, OR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$, NO_2, NR^5R^6, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, $C(=O)R^5$, $C(=NOR^5)R^6$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$ or R^8,
wherein,
R^5, R^6, R^7 and R^8 independently is H, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl,

In still another preferred embodiment,
V independently is aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl or morpholinyl optionally substituted with one or more substituents selected from the group consisting of F, Cl, CN, CF_3, =O, $=NOR^5$, $=NNR^5R^6$, OR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$, NO_2, NR^5R^6, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, $C(=O)R^5$, $C(=NOR^5)R^6$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$ or R^8,
wherein,
R^5, R^6, R^7 and R^8 independently is H, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl,

In still another preferred embodiment,
V independently is phenyl, naphtyl, thienyl, furyl, pyridyl, quinolinyl or isoquinolinyl optionally substituted with one or more substituents selected from the group consisting of F, Cl, CN, CF_3, =O, $=NOR^5$, $=NNR^5R^6$, OR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$, NO_2, NR^5R^6, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, $C(=O)R^5$, $C(=NOR^5)R^6$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$ or R^8,
wherein,
R^5, R^6, R^7 and R^8 independently is H, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl,

In still another preferred embodiment,
V independently is phenyl or naphtyl optionally substituted with one or more substituents selected from the group consisting of F, Cl, CN, CF_3, =O, $=NOR^5$, $=NNR^5R^6$, OR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$, NO_2, NR^5R^6, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, $C(=O)R^5$, $C(=NOR^5)R^6$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$ or R^8,
wherein,
R^5, R^6, R^7 and R^8 independently is H, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl,

In still another preferred embodiment,
V independently is thienyl, furyl, pyridyl, quinolinyl or isoquinolinyl optionally substituted with one or more substituents selected from the group consisting of F, Cl, CN, CF_3, =O, $=NOR^5$, $=NNR^5R^6$, OR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$, NO_2, NR^5R^6, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, $C(=O)R^5$, $C(=NOR^5)R^6$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$ or R^8,
wherein,
R^5, R^6, R^7 and R^8 independently is H, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl,

In still another preferred embodiment,
V independently is methyl, ethyl, propyl, butyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl optionally substituted with one or more substituents selected from the group consisting of F, Cl, CN, CF_3, =O, $=NOR^5$, $=NNR^5R^6$, OR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$, NO_2, NR^5R^6, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, $C(=O)R^5$, $C(=NOR^5)R^6$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$ or R^8,
wherein,
R^5, R^6, R^7 and R^8 independently is H, phenyl, naphthyl, thienyl, furyl, pyridinyl, quinolinyl or isoquinolinyl,

In still another preferred embodiment,
V independently is aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl or morpholinyl optionally substituted with one or more substituents selected from the group consisting of F, Cl, CN, CF_3, =O, $=NOR^5$, $=NNR^5R^6$, OR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$,

NO_2, NR^5R^6, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, $C(=O)R^5$, $C(=NOR^5)R^6$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$ or R^8,
wherein,
R^5, R^6, R^7 and R^8 independently is H, phenyl, naphthyl, thienyl, furyl, pyridinyl, quinolinyl or isoquinolinyl,

In still another preferred embodiment,
V independently is phenyl, naphtyl, thienyl, furyl, pyridyl, quinolinyl or isoquinolinyl optionally substituted with one or more substituents selected from the group consisting of F, Cl, CN, CF_3, =O, $=NOR^5$, $=NNR^5R^6$, OR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$, NO_2, NR^5R^6, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, $C(=O)R^5$, $C(=NOR^5)R^6$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$ or R^8,
wherein,
R^5, R^6, R^7 and R^8 independently is H, phenyl, naphthyl, thienyl, furyl, pyridinyl, quinolinyl or isoquinolinyl,

In still another preferred embodiment,
V independently is phenyl or naphtyl optionally substituted with one or more substituents selected from the group consisting of F, Cl, CN, CF_3, =O, $=NOR^5$, $=NNR^5R^6$, OR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$, NO_2, NR^5R^6, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, $C(=O)R^5$, $C(=NOR^5)R^6$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$ or R^8,
wherein,
R^5, R^6, R^7 and R^8 independently is H, phenyl, naphthyl, thienyl, furyl, pyridinyl, quinolinyl or isoquinolinyl,

In still another preferred embodiment,
V independently is thienyl, furyl, pyridyl, quinolinyl or isoquinolinyl optionally substituted with one or more substituents selected from the group consisting of F, Cl, CN, CF_3, =O, $=NOR^5$, $=NNR^5R^6$, OR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$, NO_2, NR^5R^6, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, $C(=O)R^5$, $C(=NOR^5)R^6$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$ or R^8,
wherein,
R^5, R^6, R^7 and R^8 independently is H, phenyl, naphthyl, thienyl, furyl, pyridinyl, quinolinyl or isoquinolinyl,

In still another preferred embodiment,
V independently is H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, aryl or heteroaryl

In still another preferred embodiment,
V independently is H,

In still another preferred embodiment,
V independently is C_1-C_6 alkyl, C_3-C_7 cycloalkyl or C_3-C_7 cycloheteroalkyl,

In still another preferred embodiment,
V independently is methyl, ethyl, propyl or butyl

In still another preferred embodiment
V independently is cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl

In still another preferred embodiment
V independently is aziridinyl, pyrrolidinyl, piperidinyl or morpholinyl

In still another preferred embodiment,
V independently is aryl or heteroaryl

In still another preferred embodiment,
V independently is phenyl or naphthyl

In still another preferred embodiment,
V independently is thienyl, furyl, pyridyl, quinolinyl or isoquinolyl

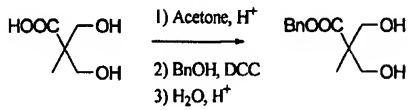
In yet another preferred embodiment,
W is selected among the group consisting of $C(=O)OR^5$, $C(O)R^5$, $C(=O)NR^5{}_2$, $C(=O)NR^5OR^6$, $C(=NR^5)OR^6$, $C(=NOR^5)\ R^6$, $C(=NNR^5{}_2)R^8$, $S(O)_2R^5$, $S(O)_2NR^5{}_2$, and –CN

In yet another preferred embodiment,

W is selected among the group consisting of $C(=O)OR^5$, $C(O)R^5$, $C(=O)NR^5_2$, $S(O)_2R^5$, $S(O)_2NR^5_2$, and -CN

Experimental section

Example 1. Synthesis of an aliphatic carboxylic acid Carrier Precursor (I):



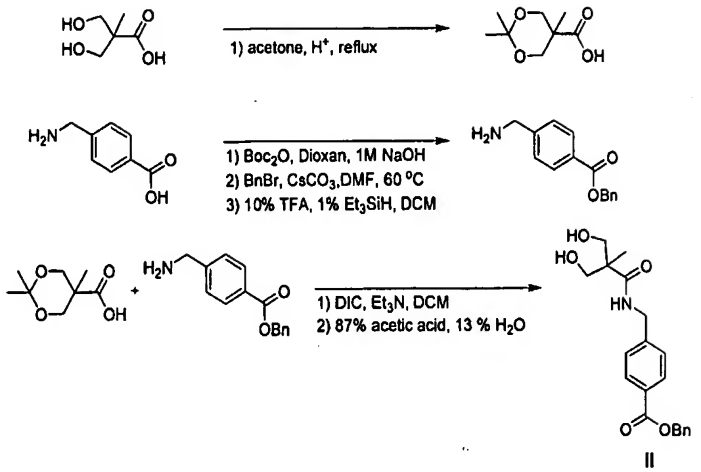
I

2,2-Bis(hydroxymethyl)-propionic acid (13.41g, 0.01 mol), acetone (200 ml, 2.72 mol), molecular sieves (10 g) and sulphuric acid (0.5 ml, catalytic amounts) were mixed in the given order at rt. The suspension was refluxed for 10 hours, then neutralized with sodium hydrogen carbonate and filtered through activated carbon on a plough of silica. Evaporation furnished 2,2,5-trimethyl-5-carboxy-1,3-dioxan as a crystalline solid 15.23 g (87%). ^{1}H-NMR (MeOH-d_4): δ 4.17 (d, 2H), 3.68 (d, 2H), 1.42(s, 3H), 1.35(s, 3H), 1.^{16}(s, 3H).

2,2,5-trimethyl-5-carboxy-1,3-dioxan (15.23 g, 87.4 mmol) was dissolved in THF (60 ml) and added DCC (dicyclohexyl carbodiimide, 18.04 g, 87.4 mmol), followed by slow addition of benzyl alcohol (9.04 ml, 87.4 mmol) at 0 °C. Stirring was continued at rt. for 18 hours. The mixture was filtered and solvent was removed by evaporation in vaccu. Distillation followed by chromatography (Ethyl acetate Heptane 1:3) gave 4.1 g of 2,2,5-trimethyl-5-carboxy-1,3-dioxan benzyl ester as crystals. ^{1}H-NMR ($CDCl_3$): δ 7.36(m, 5H), 5.20 (s, 2H) 4.24 (d, 2H), 3.67 (d, 2H), 1.47(s, 3H), 1.40(s, 3H), 1.22(s, 3H).

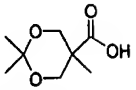
2,2,5-Trimethyl-5-carboxy-1,3-dioxan benzyl ester (4.02 g, 15.2 mmol) was dissolved in a mixture of acetone: water : acetic acid (20 ml :8 ml : 2 ml). The solution was heated at 45 °C for 10 hours and at 56 °C for additional 10 hours. The temperature was raised to 80 °C and the acetone was slowly replaced with water. Stirring was continued for 1.5 hour at 80 °C. Concentration twice from toluene gave 2,2-bis(hydroxymethyl)-propionic acid benzyl ester (I) as colourless crystals 3.40 g. ^{1}H-NMR (MeOH-d_4): δ 7.36 (m, 5H), 5.17 (s,2H), 3.73 (d, 2H), 3.67 (d, 2H), 1.20 (s, 3H).

Example 2. Synthesis of a benzoic acid Carrier Precursor (II):



II

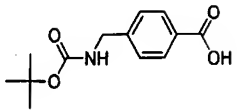
Isopropylidene-2,2-bis(hydroxymethyl)propionic acid:



2,2-Bis(hydroxymethyl)propionic acid (0.12 mol, 15.9 g) was refluxed in acetone (250 mL) with molecular sieves and conc. sulphuric acid (0.5 mL) for 10 hours. The reaction mixture was then neutralised with $NaHCO_3$ (1M aq.), stirred with activated charcoal and filtered. The product was collected as a white crystalline upon concetration of the solvent.

Yield 50 % (10.5g): ^{1}H-NMR (DMSO-d_6): 1.07 (s, 3H, -CH_3); 1.26 (s, 3H, -CH_3); 1.34 (s, 3H, -CH_3); 3.53 and 3.57 (d, 2H, -CH_2-); 3.99 and 4.02 (d, 2H, -CH_2-).

4-(Boc-amino-methyl)-benzoic acid:

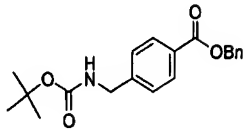


4-Methylaminobenzoic acid was dissolved in dioxane (10 mL) and NaOH (22 mL, 1M solution) and cooled to 0 °C. Ditertbutyl dicarbonate (10 mmol, 2.18 g) and

NaOH (8 mL, 2M solution) was added, and the reaction mixture was left over night at room temperature. Half of the solvent was removed under reduced pressure and ethylacetate added (25 mL). The reaction mixture was then neutralised by adding HCl (2 M solution) to pH = 4, and extracted with ethyl acetate (3×75 mL). The organic phase was dried, and evaporated to dryness, and the product was obtained as a white crystalline solid.

Yield: 65 % (6.0 mmol, 1.51 g): ^{1}H-NMR (DMSO-d_6): 12.84 (s, 1H); 7.89 (d, 2H); 7.46 (t, 1H); 7.34 (d, 2H); 4.19 (d, 2H); 1.40 (s, 9H).

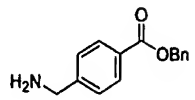
4-[(Boc-amino)-methyl]-benzoic acid benzyl ester:



4-[(Boc-amino)-methyl]-benzoic acid (5.89 mmol, 1.48 g) in anhydrous DMF (20 mL) was added Cs_2CO_3 (2.95 mmol, 0.96 g) and stirred for 1h at room temperature. Benzyl bromide (8.2 mmol, 1.0 mL) was added, and the reaction stirred for 9 hours. The solvent was removed under reduced pressure, and the crude was suspended in water (100 mL) and extracted with diethyl ether (3×100 mL). The organic phase was then dried, evaporated to dryness and the obtained product was purified using dry column vacuum chromatography.

Yield = 81 % (4.79 mmol, 1.56 g): ^{1}H-NMR (DMSO-d_6): 7.95 (d, 2H); 7.48-7.37 (m, 7H); 5.35 (s, 2H); 4.20 (d, 2H); 1.39 (s, 9H).

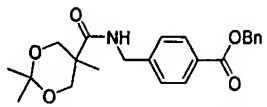
4-Methylamino benzoic acid benzyl ester:



N-Boc-4-methylamino benzoic benzyl ester (4.79 mmol, 1.55 g) was dissolved in DCM (25 mL) with TFA (10 % v/v) and triethylsilane (1 % v/v) and stirred for 30 minutes. The solvent was removed under reduced pressure and the product purified using dry column vacuum chromatography.

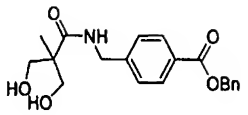
Yield = 47 % (2.28 mmol, 550 mg): ^{1}H-NMR (DMSO-d_6): 8.69 (s, 2H); 8.03 (d, 2H); 7.62 (d, 2H); 7.50-7.36 (m, 5H); 5.37 (s, 2H); 4.14 (s, 2H).

4-{[(2,2,5-Trimethyl-[1,3]dioxane-5-carbonyl)-amino]-methyl}-benzoic acid benzyl ester



Isopropylidene-2,2-bis(hydroxymethyl)propionic acid (4.10 mmol, 714 mg) and 4-methylamino benzyloxy benzoic acid (4.14 mmol, 1.0 g) in DCM (20 mL) was cooled to 0 °C and diisopropyl carbodiimide (5.5 mmol, 0.7 mL) was added. The reaction mixture was left over night at room temperature, and the solvent was removed under reduced pressure. The crude was dissolved in toluene and filtered. The filtrate was purified using Dry Column Vacuum Chromatography.
Yield = 29 % (478 mg): ^{1}H-NMR (DMSO-d_6): 8.25 (t, 1H); 7.93 (d, 2H); 7.47-7.35 (m, 9H); 5.34 (s, 2H); 4.39 (d, 2H); 4.04 (d, 2H); 3.65 (d, 2H); 1.37 (s, 3H); 1.29 (s, 3H); 1.05 (s, 3H);

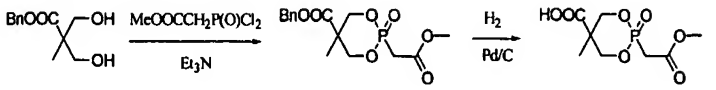
4-[(3-Hydroxy-2-hydroxymethyl-2-methyl-propionylamino)-methyl]-benzoic acid benzyl ester



II

4-{[(2,2,5-Trimethyl-[1,3]dioxane-5-carbonyl)-amino]-methyl}-benzoic acid benzyl ester (1.2 mmol, 478 mg) was dissolved in acetic acid (11.5 mL, 87 % v/v) and stirred at 40 °C for 3 hours. The product II was obtained by evaporation of the reaction mixture under reduced pressure and co evaporation from anhydrous toluene (3×20 mL).
Yield = 90 %: ^{1}H-NMR (DMSO-d_6): 8.07 (t, 1H); 7.92 (d, 2H); 7.48-7.12 (m, 7H); 5.34 (s, 2H); 4.72 (bs, 2H); 4.37 (d, 2H); 3.46 (m, 4H); 1.04 (s, 3H).

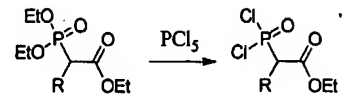
Example 3.Synthesis of an aliphatic carboxylic acid Carrier-Functional entity precursor ensemble (III):



III

2,2-Bis(hydroxymethyl) propionic acid benzyl ester (1.01 g, 4.5 mmol) was dissolved in toluene (10 ml) and triethylamine (0.75 ml, 1.2 eq.). Methyl dichlorophosphosphorylacetate (0.55 ml, 0.45 mmol, prepared according to the procedure described in *J. Org. Chem.* (1997), **62**, 1934-39) was added slowly at 0 °C. Stirring was continued at 0 °C for 15 min. and at rt. for 60 min. The precipitate was filtered of and the filtrate was diluted with ethylacetate (30 ml) and successively washed with, 1 M citric acid (10 ml), 1M sodium hydroxide (2 x 10 ml), saturated ammonium chloride (2 x 10 ml) and saturated sodium chloride (2 x 10 ml), dried with magnesium sulphate and evaporation gave 1.00 g crude material. Purification on silica EtOAc Heptane 1:1 → EtOAc furnished 300 mg of a diastereomeric mixture of 2-methoxycarbonylmethyl-5-methyl-2-oxo-2l5-[1,3,2]dioxaphosphinane-5-carboxylic acid benzyl ester. A) ^{1}H-NMR ($CDCl_3$): δ 7.36 (m, 5H), 5.21 (s, 2H), 4.80 (t, 2H), 4.21 (t, 2H), 3.77 (s, 3H), 3.15 (d, 2H), 1.32 (s, 3H). B) ^{1}H-NMR ($CDCl_3$): δ 7.36 (m, 5H), 5.24 (s, 2H), 4.68 (dd, 2H), 4.37 (dd, 2H), 3.73 (s, 3H), 2.99 (d, 2H), 1.20 (s, 3H).
2-Methoxycarbonylmethyl-5-methyl-2-oxo-2l5-[1,3,2]dioxaphosphinane-5-carboxylic acid benzyl ester (100 mg, 0.29 mmol, diastereomer A) was dissolved in methanol (5 ml) and placed inside an autoclave. Air was replaced with argon and the catalyst was added (5% Pd/C, 10 mg). The reaction was stirred in a H_2 atmosphere (50 bar) at rt. for 18 hours. The catalyst was filtered of and the solvent removed to give 71 mg of 2-methoxycarbonylmethyl-5-methyl-2-oxo-2l5-[1,3,2]dioxaphosphinane-5-carboxylic acid (III), as colourless crystals. ^{1}H-NMR (D_2O) : δ 4.74 (d, 2H), 4.35 (dd, 2H), 3.72 (s, 3H), 3.41 (d, 2H), 1.10 (s, 3H)

Example 4: Synthesis of a benzoic acid Carrier-Functional entity precursor ensembles(IV):

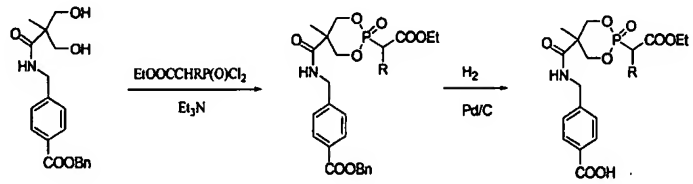


PCl_5 (75 mmol) was added to the phosphonate ester(30.0 mmol) at 0 °C. After stirring for 15 min. the temperature was raised to 75 °C for 10 hours. The reaction was

followed by ^{31}P-NMR. Distillation at reduced pressure yielded the corresponding dichloride products in 40-50% yield.

Ethyl 2-(dichlorophosphoryl)propionate (bp at 4 mbar: 123 – 125 °C). MS found m/e 219 $[M+H]^+$

Ethyl 2-(dichlorophosphoryl)butyrate (bp at 4 mbar: 125 – 127 °C). MS found m/e 233 $[M+H]^+$)



IV

4-[(3-Hydroxy-2-hydroxymethyl-2-methyl-propionylamino)-methyl]-benzoic acid benzyl ester (1 mmol) was dissolved in toluene triethylamine (2.5 mmol), heating required. The solution was cooled until a precipitate emerged and solution of alkyl 2-(dichlorophosphoryl)carboxylate (1 mmol) in toluene was added. The mixture was stirred at 0 °C for approximately 2 hours and left at rt over night. Ethylacetate (20 mL) was added and the precipitated triethyl ammonium chloride was filtered off. The filtrate was subsequently washed with citric acid (1M, 10 ml), sodium hydroxide (1M, 2 x 10 ml), saturated ammonium chloride (10 ml), dried with magnesium sulphate and evaporated to an oil which was purified by HPLC 0.1%HCCOH, 99.9% H_2O → 0.1% HCCOH, 99.9% MeCN. Fractions containing the desired mass were collected and evaporated to give the desired products in 40-50% yield

4-({[2-(1-Ethoxycarbonyl-ethyl)-5-methyl-2-oxo-2λ^5-[1,3,2]dioxaphosphinane-5-carbonyl]-amino}-methyl)-benzoic acid benzyl ester: MS m/e 504 $[M+1]^+$

4-({[2-(1-Ethoxycarbonyl-propyl)-5-methyl-2-oxo-2λ^5-[1,3,2]dioxaphosphinane-5-carbonyl]-amino}-methyl)-benzoic acid benzyl ester: MS m/e 518 $[M+1]^+$

Debenzylation were performed by dissolving the purified benzylesters (0.5 mmol) in methanol (5 ml) and placed inside an autoclave. Air was replaced with argon and the catalyst was added (20% Pd/C, 50 mg). The reaction was stirred in a H_2 atmosphere (60 bar) at 40 °C for 2 hours. The catalyst was filtered off and the solvent removed *in vacuo*. The pure products were obtained by HPLC purification using 0.1%HCCOH, 99.9% H_2O → 0.1% HCCOH, 99.9% MeCN. Fractions containing the desired mass were collected and evaporated to dryness.

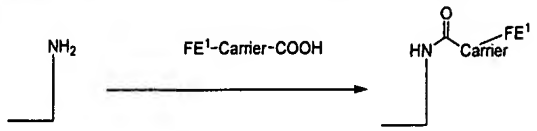
Example 4a

4-({[2-(1-Ethoxycarbonyl-ethyl)-5-methyl-2-oxo-2λ^5-[1,3,2]dioxaphosphinane-5-carbonyl]-amino}-methyl)-benzoic acid: MS m/e 414 $[M+1]^+$

Example 4b

4-({[2-(1-Ethoxycarbonyl-propyl)-5-methyl-2-oxo-2λ^5-[1,3,2]dioxaphosphinane-5-carbonyl]-amino}-methyl)-benzoic acid: MS m/e 428 $[M+1]^+$

General Procedure 1: Preparation of building blocks by loading a Carrier-Functional entity ensemble onto a nucleotide derivative comprising an amino group:



15 µL of a 150 mM building block solution of FE^1-Carrier-COOH is mixed with 15 µL of a 150 mM solution of EDC and 15 µL of a 150 mM solution of N-hydroxysuccinimide (NHS) using solvents like DMF, DMSO, water, acetonitril, THF, DCM, methanol, ethanol or a mixture thereof. Optionally, the NHS is replaced by a base such as TEA, DIEA, pyridine or DMAP. The mixture is left for 15 min at 25°C. 45 µL of an aminooligo (10 nmol) in 100 mM buffer at a pH between 5 and 10, preferably 6.0-7.5 is added and the reaction mixture is left for 2 hours at 25°C. Excess building block and organic by-products were removed by extraction with EtOAc (400 µL). Remaining EtOAc is evaporated *in vacuo* using a speedvac. The building block is purified following elution through a BioRad micro-spin chromatography column, and analyzed by electron spray mass spectrometry (ES-MS).

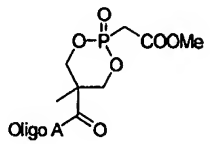
Aminooligo's used:

A: 5'-CTA GGG ACG AGC ATC CAT CG **X**

X = Amino-C2-dT phosphate (Glen catalogue # 10-1037-)

Example 5 (General Procedure 1)

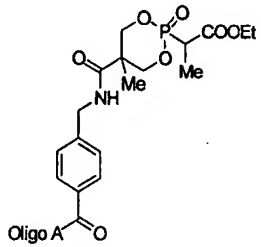
Oligo A with 5' Biotin (Glen catalogue # 10-5950) loaded with Example **3**



MS (calc.) = 7246.92; MS (found) = 7246.97

Example 6 (General Procedure 1)

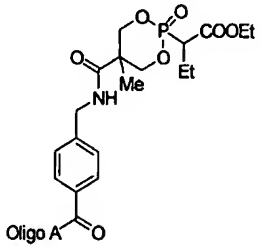
Oligo A loaded with example **4a**



MS (calc.) = 7004.71; MS (found) = 7002.03

Example 7 (General Procedure 1)

Oligo A loaded with example **4b**



MS (calc.) = 7018.74; MS (found) = 7016.52

Use of building blocks

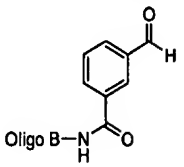
Loading of a carbonyl containing scaffolds on an oligonucleotide containing an amino group:

25 µL of a 150 mM carbonyl containing benzoic acid derivative in DMF was mixed with 25 µL of a 150 mM solution of EDC in DMF. The mixture was left for 30 min at 25°C. 50 µL of an aminooligo (10 nmol) in 100 mM HEPES buffer pH 7.5 was added and the reaction mixture was left for 20 min at 25°C. The excess building block was removed by extraction with EtOAc (500 µL) and remaining EtOAc was removed *in vacuo* by spinning 10 min in a speedvac. The aminooligo loaded with the benzoic acid derivative was ethanol precipitated twice using NH_4OAc and analysed by electron spray mass spectrometry (ES-MS).

B: 5'- **X**CGATGGATGCTCGTCCCTAG

X = 5'-amine-C6 (Glen catalogue # 10-1906-)

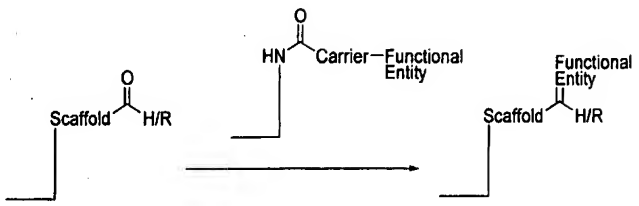
Loading of 3-formyl benzoic acid scaffold on oligo B:



V

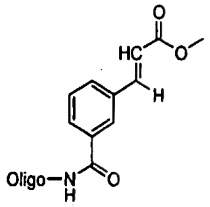
MS (calc.) = 6420.32 MS (found) = 6418.59

<u>General Procedure 2: Transfer of a functional entity from a building block to a scaffold carrying a reactive recipient group:</u>



An oligonucleotide loaded with a phosphonate ester derivative is combined at 10 µM final concentration with one equivalent of a complementary DNA template displaying an aldehyde or ketone. Olefination proceeds at 37 °C for 12 hours in 50 mM sodium borate, pH 9 buffer. Organic by-products are removed by extraction with EtOAc (400 µL), followed by evaporation of residual organic solvent for 10 min *in vacuo* using a speedvac. Oligonucleotides are isolated by eluting sample through a BioRad micro-spin chromatography column. Products are characterized by ES-MS analysis.

Example 8 (General Procedure 2)

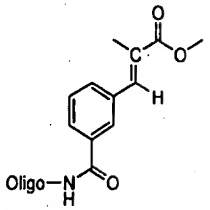


Oligo = Oligo B

The compound was obtained reacting example **5** with scaffold oligo **V**

MS (calc.) = 6476.39 MS (found) = 6474.29

Example 9 (General Procedure 2)

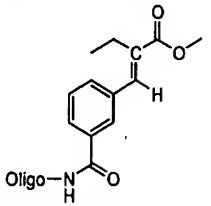


Oligo = Oligo B

The compound was obtained reacting example **6** with scaffold oligo **V**

MS (calc.) = 6504.44.## MS (found) = 6502.65

Example 10 (General Procedure 2)



Oligo = Oligo B

The compound was obtained reacting example **7** with scaffold oligo **V**

MS (calc.) = 6518.47 MS (found) = 6516.08

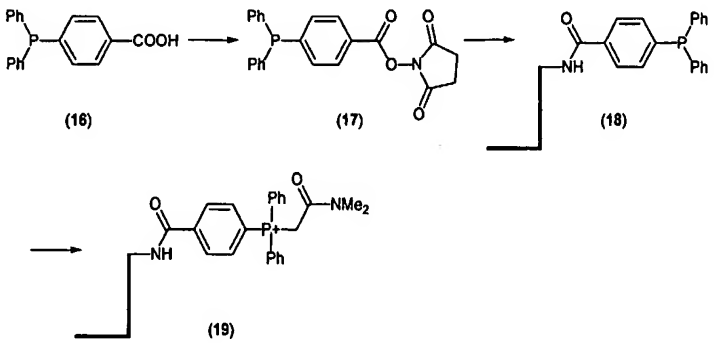
Model Example 11. General route to the formation of Wittig and HWE monomer building blocks and use of these:

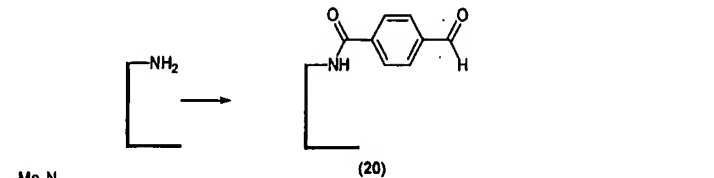
Commercially available building block (**16**) may be transformed into the NHS ester (**17**) by standard means, *i.e.* DCC or DIC couplings.

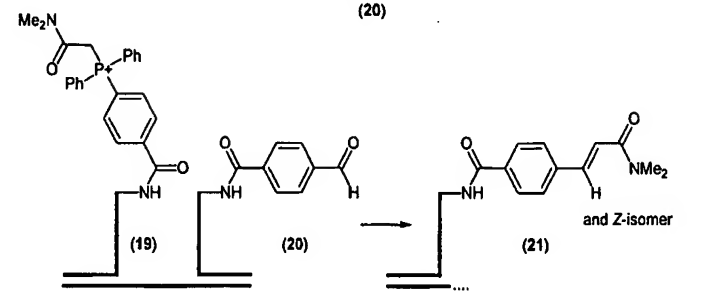
An amine carrying oligonucleotide in buffer 50 mM MOPS or hepes or phosphate pH 7.5 is treated with a 1-100 mM solution and preferably 7.5 mM solution of the organic building block in DMSO or alternatively DMF, such that the DMSO/DMF concentration is 5-50%, and preferably 10%. The mixture is left for 1-16 h and preferably 2-4 h at 25 °C. To give the phosphine bound monomer building block (**18**). This monomer building block is further transformed by addition of the appropriate alkylhalide, e.g. *N,N*-dimethyl-2-iodoacetamide as a 1-100 mM and preferably 7.5 mM solution in DMSO or DMF such that the DMSO/DMF concentration is 5-50%, and preferably 10%. The mixture is left for 1-16 h and preferably 2-4 h at 25 °C. To give the monomer building block (**19**). Alternative to this, may the organic building block (**17**) be *P*-alkylated with an alkylhalide and then be coupled onto an amine carrying oligonucleotide to yield (**19**).

An aldehyde bound monomer building block (**20**), e.g. formed by the reaction between the NHS ester of 4-formylbenzoic acid and an amine carrying oligonucleotide,

using conditions similar to those described above, will react with (**19**) under slightly alkaline conditions to yield the alkene (**21**).





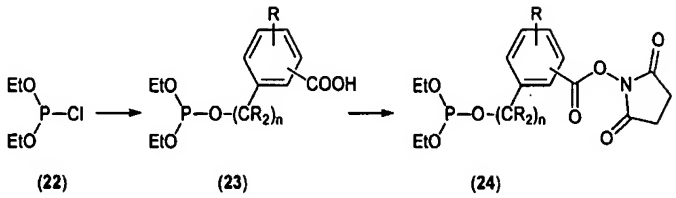


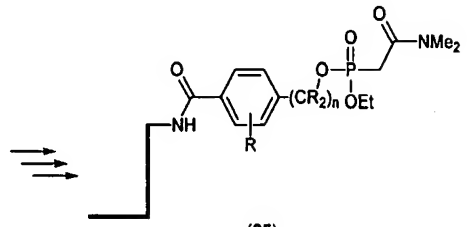
The reaction of monomer building blocks (**19**) and (**20**) may be conducted as follows:

The template oligonucleotide (1 nmol) is mixed with monomer building block (**19**) (1 nmol) and (**20**) (1 nmol) in 0.1 M TAPS, phosphate or hepes-buffer and 1 M NaCl solution, pH=7.5-8.5 and preferably pH=8.0. The reaction mixture is left at 35-65 °C preferably 58 °C over night to yield template bound (**21**).

As an alternative to (**17**) phosphonates (**24**) may be used instead. They may be prepared by the reaction between diethylchlorophosphite (**22**) and the appropriate car-

boxy carrying alcohol. The carboxylic acid is then transformed into the NHS ester (**24**) and the process and alternatives described above may be applied. Although instead of a simple *P*-alkylation, the phosphite will undergo Arbuzov's reaction and generate the phosphonate. Monomer building block (**25**) benefits from the fact that it is more reactive than its phosphonium counterpart (**19**).





Abbreviations

DCC	N,N'-Dicyclohexylcarbodiimide
DIC	Diisopropylcarbodiimide
DIEA	Diisopropylethylamine
TEA	Triethylamin
DNA	Deoxyribosenucleic Acid
EDC	1-Ethyl-3-(3'-dimethylaminopropyl)carbodiimide·HCl
LNA	Locked Nucleic Acid
NHS	N-hydroxysuccinimid
PNA	Peptide Nucleic Acid
RNA	Ribonucleic acid
RP-HPLC	Reverse Phase High Performance Liquid Chromatography
ES-MS	Electron spray mass spectrometry
DMF	Dimethylformamide
THF	Tetrahydrofuran

Claims

1. A building block of the general formula

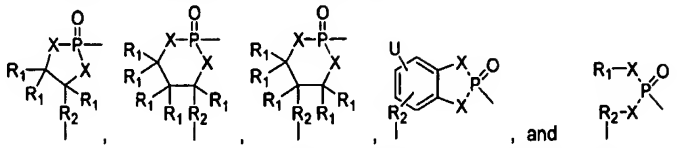
Complementing Element – Linker – Carrier – Functional entity precursor

capable of transferring a functional entity precursor to a recipient reactive group, wherein

Complementing Element is a group identifying the functional entity,

Linker is a chemical moiety comprising **a spacer** and a **S-C-connecting group**, wherein the spacer is a valence bond or a group distancing the functional entity precursor to be transferred from the complementing element and the S-C-connecting group connects the spacer with the Carrier,

Carrier is selected among the groups consisting of



wherein the Functional entity precursor is attached to the phosphorous atom,

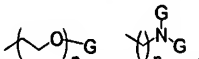
each individual X is chosen independently among the group consisting of NR^{16},O, S, and Se;

U = R^3;

R^1 = H, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl C_2-C_6 alkenyl, C_2-C_6 alkynyl, aryl or heteroaryl; optionally substituted with one or more F, Cl, Br, I, or CN, and where each of the individual R^1 groups are chosen independently;

R^2 = a valence bond, C_1-C_6 Alkylene, C_2-C_6 Alkenylene, C_2-C_6 Alkynylene, Arylene, Heteroarylene, C_1-C_6 Alkylene-arylene or C_1-C_6 Alkylene-heteroarylene;

R^3 is selected from -H, -OR^4, -NR^4_2, - F, -Cl, -Br, -I, -NO_2, -CN, -C(Halogen)$_3$, -C(O)R^4, -C(O)NHR^4, C(O)NR^4_2, -NC(O)R^4, -S(O)$_2$NHR^4, -S(O)$_2$NR^4_2, -S(O)$_2R^4$, –P(O)$_2$-R^4, –P(O)-R^4, –S(O)-R^4, P(O)-OR^4, –S(O)-OR^4, -$N^+R^4_3$, wherein and each individual R^4 is chosen independently from H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or aryl,

R^{16} is selected independently from H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, aryl, C_1-C_6 alkylene-aryl,  or , G is H or C_1-C_6 alkyl and n is 1,2,3 or 4.

Functional entity precursor is of the general formula C(H)(V)-W;

wherein V independently is H, alkyl, alkenyl, alkynyl, alkadienyl, cycloalkyl, cycloheteroalkyl, aryl or heteroaryl, optionally substituted with one or more substituents selected from the group consisting of $SnR^5R^6R^7$, $Sn(OR^5)R^6R^7$, $Sn(OR^5)(OR^6)R^7$, BR^5R^6, $B(OR^5)R^6$, $B(OR^5)(OR^6)$, halogen, CN, CNO, $C(halogen)_3$, =O, $=NOR^5$, $=NNR^5R^6$, OR^5, $OC(=O)R^5$, $OC(=O)OR^5$, $OC(=O)NR^5R^6$, SR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$, NO_2, N_3, NR^5R^6, $N^+R^5R^6R^7$, NR^5OR^6, $NR^5NR^6R^7$, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, NC, $P(=O)(OR^5)OR^6$, $P^+R^5R^6R^7$, $C(=O)R^5$, $C(=NR^5)R^6$, $C(=NOR^5)R^6$, $C(=NNR^5R^6)$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$, $C(=O)NR^5NR^6R^7$, $C(=NR^5)NR^6R^7$, $C(=NOR^5)NR^6R^7$ or R^8,

wherein,

R^5, R^6 and R^7 independently is H, alkyl, alkenyl, alkynyl, alkadienyl, cycloalkyl, cycloheteroalkyl, aryl or heteroaryl, optionally substituted with one or more substituents selected from the group consisting of halogen, CN, CNO, $C(halogen)_3$, =O, $=NOR^5$, $=NNR^5R^6$, OR^8, $OC(=O)R^8$, $OC(=O)OR^8$, $OC(=O)NR^8R^9$, SR^8, $S(=O)R^8$, $S(=O)_2R^8$, $S(=O)_2NR^8R^9$, NO_2, N_3, NR^8R^9, $N^+R^8R^9R^{10}$, NR^5OR^6, $NR^5NR^6R^7$, $NR^8C(=O)R^9$, $NR^8C(=O)OR^9$, $NR^8C(=O)NR^9R^{10}$, NC, $P(=O)(OR^8)OR^9$, $P^+R^5R^6R^7$, $C(=O)R^8$, $C(=NR^8)R^9$, $C(=NOR^8)R^9$, $C(=NNR^8R^9)$, $C(=O)OR^8$, $C(=O)NR^8R^9$, $C(=O)NR^8OR^9$ $C(=NR^5)NR^6R^7$, $C(=NOR^5)NR^6R^7$or $C(=O)NR^8NR^9R^{10}$, wherein R^5 and R^6 may together form a 3-8 membered heterocyclic ring or R^5 and R^7 may together form a 3-8 membered heterocyclic ring or R^6 and R^7 may together form a 3-8 membered heterocyclic ring,

wherein,

R^8, R^9 and R^{10} independently is H, alkyl, alkenyl, alkynyl, alkadienyl, cycloalkyl, cycloheteroalkyl, aryl or heteroaryl and wherein R^8 and R^9 may together form a 3-8 membered heterocyclic ring or R^8 and R^{10} may together form a 3-8 membered heterocyclic ring or R^9 and R^{10} may together form a 3-8 membered heterocyclic ring.

W is selected among the group consisting of H, aryl, heteroaryl, $C(=O)OR^{11}$, $C(O)R^{11}$, $C(=O)NR^{11}{}_2$, $C(=O)NR^{11}OR^{11}$, $C(=NR^{11})OR^{11}$, $C(=NOR^{11})R^{11}$, $C(=NNR^{11}{}_2)R^{11}$, $S(O)R^{11}$, $S(O)_2R^{11}$, $S(O)NR^{11}{}_2$, $S(O)_2NR^{11}{}_2$, -CN, $P(O)R^{11}{}_2$, $-NO_2$, $NR^{11}{}_3{}^+$ or $SR^{11}{}_2{}^+$

where each individual R^{11} is H or selected independently among the group consisting of C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, aryl, heteroaryl, said group being substituted with 0-3 R^{12} and 0-3 R^{15} and

each individual R^{12} is selected independently from $-N_3$, -CNO, $-C(NOH)NH_2$, -NHOH, $-NHR^4NHR^4$, $-C(O)R^4$, $-SnR^4{}_3$, $-B(OR^4)_2$, $-P(O)(OR^4)_2$ or the group consisting of C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_4-C_8 alkadienyl said group being substituted with 0-2 R^{13},

where each individual R^{13} is independently selected from $-NO_2$, $-C(O)OR^{14}$, $-C(O)R^{14}$, -CN, $-OSiR^{14}{}_3$, $-OR^{14}$ and $-NR^{14}{}_2$,

each individual R^{14} is independently chosen from a group comprising H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, aryl or C_1-C_6 alkylene-aryl substituted with 0-3 substituents independently selected from –F, -Cl, $-NO_2$, $-R^4$, $-OR^4$, $-SiR^4{}_3$,

R^{15} is =O, -F, -Cl, -Br, -I, -CN, $-NO_2$, $-OR^{14}$, $-NR^{14}{}_2$, $-NR^{14}$-$C(O)R^{14}$, $-NR^{14}$-$C(O)OR^{14}$, $-SR^{14}$, -S(O) R^{14}, $-S(O)_2R^{14}$, $-COOR^{14}$, $-C(O)NR^{14}{}_2$ and $-S(O)_2NR^{14}{}_2$.

2. The compound according to claim 1 wherein the **Functional entity precursor** is of the general formula C(H)(V)-W; in which V is H, -F, -Cl, -Br, -I, -CN, $-NO_2$ or $-OR^{14}$, or selected among the group consisting of C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_4-C_8 alkadienyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, aryl, heteroaryl, -O-aryl and –O-heteroaryl said group being substituted with 0-3 R^{11}, 0-3 R^{12} and 0-3 R^{15};

or V is C_1-C_3 alkylene-$NR^{11}{}_2$, C_1-C_3 alkylene-$NR^{11}C(O)R^{14}$, C_1-C_3 alkylene-$NR^{11}C(O)OR^{14}$, C_1-C_2 alkylene-O-$NR^{11}{}_2$, C_1-C_2 alkylene-O-$NR^{11}C(O)R^{14}$, C_1-C_2 alkylene-O-$NR^{11}C(O)OR^{14}$ substituted with 0-3 R^{15};

W is selected among the group consisting of H, aryl, heteroaryl, $C(=O)OR^{11}$, $C(O)R^{11}$, $C(=O)NR^{11}{}_2$, $C(=O)NR^{11}OR^{11}$, $C(=NR^{11})OR^{11}$, $C(=NOR^{11})R^{11}$, $C(=NNR^{11}{}_2)R^{11}$, $S(O)R^{11}$, $S(O)_2R^{11}$, $S(O)NR^{11}{}_2$, $S(O)_2NR^{11}{}_2$, -CN, $P(O)R^{11}{}_2$, $-NO_2$, $NR^{11}{}_3{}^+$ or $SR^{11}{}_2{}^+$

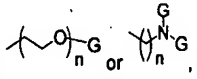
where R^{11} is H or selected independently among the group consisting of C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, aryl, heteroaryl, said group being substituted with 0-3 R^{12} and 0-3 R^{15} and

R^{12} is selected independently from $-N_3$, -CNO, $-C(NOH)NH_2$, -NHOH, $-NHR^4NHR^4$, $-C(O)R^4$, $-SnR^4{}_3$, $-B(OR^4)_2$, $-P(O)(OR^4)_2$ or the group consisting of C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_4-C_8 alkadienyl said group being substituted with 0-2 R^{13},

where R^{13} is independently selected from $-NO_2$, $-C(O)OR^{14}$, $-C(O)R^{14}$, -CN, $-OSiR^{14}{}_3$, $-OR^{14}$ and $-NR^{14}{}_2$.

R^{14} is independently chosen from a group comprising H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, aryl or C_1-C_6 alkylene-aryl substituted with 0-3 substituents independently selected from –F, -Cl, $–NO_2$, $-R^4$, $-OR^4$, $-SiR^4_3$

R^{15} is =O, -F, -Cl, -Br, -I, -CN, $-NO_2$, $-OR^{14}$, $-NR^{14}_2$, $-NR^{14}$-C(O)R^{14}, $-NR^{14}$-C(O)OR^{14}, $-SR^{14}$, -S(O) R^{14}, $-S(O)_2R^{14}$, $-COOR^{14}$, $-C(O)NR^{14}_2$ and $-S(O)_2NR^{14}_2$,

R^{16} is selected independently from H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, aryl, C_1-C_6 alkylene-aryl,  or , G is H or C_1-C_6 alkyl and n is 1,2,3 or 4.

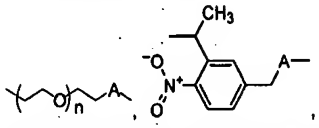
3. A compound according to claim 2 wherein W is selected among the group consisting of H, aryl, heteroaryl, $COOR^{11}$, S(O) R^{11}, $S(O)_2R^{11}$, S(O)NHR^{11}, S(O)NR^{11}_2, CN, P(O) R^{11}_2, $NR^{11}_3{}^+$ or $SR^{11}_2{}^+$.

4. A compound according to claim 2 wherein W is selected among the group consisting of C(=O)OR^{11}, C(O)R^{11}, C(=O)NR^{11}_2, $S(O)_2R^{11}$, $S(O)_2NR^{11}_2$, or –CN

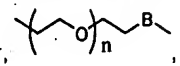
5. A compound according to any of claims 2 - 4 wherein V is C_1-C_6 alkyl, aryl or heteroaryl said group being substituted with 0-3 R^{11}, 0-3 R^{12} and 0-3 R^{15} or V is C_1-C_3 alkylene-NR^{11}C(O)R^{14} or C_1-C_3 alkyl-ene-NR^{11}C(O)OR^{14} substituted with 0-3 R^{15};

6. A compound according to any of claims 2-5 wherein R^{11} is H or selected independently among the group consisting of C_1-C_6 alkyl, C_3-C_7 cycloalkyl, aryl, or heteroaryl, said group being substituted with 0-3 R^{12} and 0-3 R^{15}

7. A compound according to claim 1 or 2 wherein **Spacer** is -A-, a group C_1-C_6 alkylene-A-, C_2-C_6 alkenylene-A-, or C_2-C_6 alkynylene-A- optionally substituted with 1 to 3 hydroxy groups, or



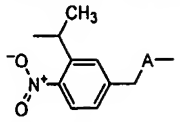
said spacer being connected through A to a moiety selected from

-B-, —$(CH_2)_n$–B—,  , and

—$(CH_2)_n$–S–S–$(CH_2)_m$–B—

where A is a valence bond, $-NR^{16}$-, –C(O)NR^{16}-, - NR^{16}-C(O)-, -O-, -S-, -C(O)-O- or –OP(=O)(O^-)-O-; B is a valence bond, -O-, -S-, $–NR^{16}$-, -C(O)- or –C(O)NR^{16}- and connects to S-C-connecting group; and n and m independently are integers ranging from 1 to 10.

8. A compound according to claim 1 or 2 wherein **Spacer** is a valence bond, C_1-C_6 alkylene-A-, C_2-C_6 alkenylene-A-, C_2-C_6 alkynylene-A-, or



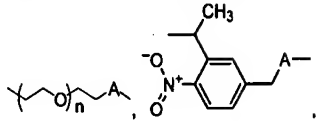
said spacer optionally being connected through A to a moiety selected from

—$(CH_2)_n$–B—,  , and

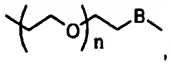
—$(CH_2)_n$–S–S–$(CH_2)_m$–B—

where A is a valence bond, –C(O)NR^{16}-, $-NR^{16}$-, -O-, -S-, or -C(O)-O-; B is a valence bond, -O-, -S-, $–NR^{16}$- or –C(O)NR^{16}- and connects to S-C-connecting group; R^{16} is selected independently from H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, aryl or C_1-C_6 alkylene-aryl and n and m independently are integers ranging from 1 to 10.

9. A compound according to claim 1 or 2, wherein the **spacer** is -A-, C_1-C_6 alkylene-A-, C_2-C_6 alkenylene-A,



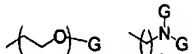
said spacer being connected through A to a moiety selected from

-B-, —$(CH_2)_n$–B—,  , or

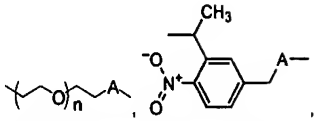
—$(CH_2)_n$–S–S–$(CH_2)_m$–B—

where A is a valence bond, $-NR^{16}$-, –C(O)NR^{16}-, $-NR^{16}$-C(O)-, -O-, -S-, -C(O)-O-, or –OP(=O)(O^-)-O-; B is a valence bond, -S-, $–NR^{16}$-, or -C(O)- and connects to S-C-connecting group;

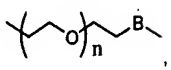
n and m independently are integers ranging from 1 to 10 and

R^{16} is selected independently from H,  or , wherein G is H or C_1-C_6 alkyl.

10. A compound according to claim 1 or 2, wherein the **spacer** is -A-, C_2-C_6 alkenylene-A,

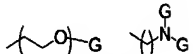
 ,

said spacer being connected through A to a moiety selected from

-B-, or —$(CH_2)_n$—B—,  ,

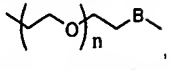
where A is a valence bond, –C(O)NR^{16}-, -NR^{16}-C(O)-, -O-, -S-, -C(O)-O-, or –OP(=O)(O^-)-O-; B is a valence bond, -S-, –NR^{16}-, or -C(O)- and connects to S-C-connecting group;

n and m independently are integers ranging from 1 to 10 and

R^{16} is selected independently from H,  or , wherein G is H or C_1-C_6 alkyl.

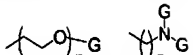
11. A compound according to claim 1 or 2, wherein the **spacer** is C_2-C_6 alkenylene-A,

said spacer being connected through A to a moiety selected from

-B-, or —$(CH_2)_n$—B—,  ,

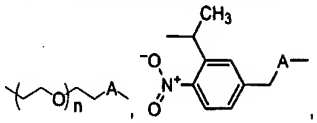
where A is a valence bond, –C(O)NR^{16}-, -NR^{16}-C(O)-, -S-, -C(O)-O- or –OP(=O)(O^-)-O-; B is a valence bond, -S-, –NR^{16}-, or -C(O)- and connects to S-C-connecting group;

n and m independently are integers ranging from 1 to 10 and

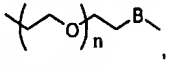
R^{16} is selected independently from H,  or , wherein G is H or C_1-C_6 alkyl; and the spacer is connected to the complementing element through a nucleobase.

12. A compound according to any of the claims 1 to 11 , wherein the spacer is attached to the 5-position of a pyrimidine type nucleobase or the 7-position of a purine or 7-deaza-purine type nucleobase.

13. A compound according to claim 1 or 2, wherein the **spacer** is -A-,

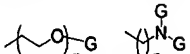
 ,

said spacer being connected through A to a moiety selected from

-B-, or —$(CH_2)_n$—B—,  ,

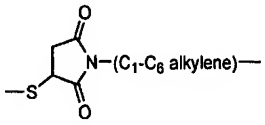
where A is a valence bond, -NR^{16}-C(O)-, -O-, or -S-; B is a valence bond, -S-, -NR^{16}-, or -C(O)- and connects to S-C-connecting group;

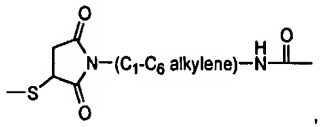
n and m independently are integers ranging from 1 to 10 and

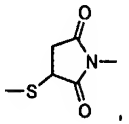
R^{16} is selected independently from H,  or , wherein G is H or C_1-C_6 alkyl; and the spacer is connected to the complementing element via a phosphorus group.

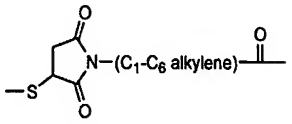
14. A compound according to claim 13, wherein the phosphorus group is a phosphate or thiophosphate group attached to a 3' or 5' end of a complementing element.

15. A compound according to claims 1 to 14, wherein the **S-C-connecting group** is a valence bond, –NH-C(=O)-, –NH-C(=O)-C_1-C_6 alkylene-, -S-S-, -S-S-C_1-C_6 alkylene-, -C_1-C_6 alkylene-S-S -, -C(=O)-NH-(C_1-C_6 alkylene)-,

 ,

 ,

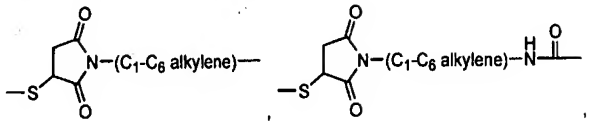
 ,

 ,

-NH-C(=O)-Arylene-C(R^{16})$_2$-NH-C(=O)-, -C(=O)-, -C(=O)-C_1-C_6 alkylene- or -C(=O)-

Arylene-$C(R^{16})_2$-NR^{16}-C(=O)-, where the right hand side of the formulae connects to the carrier.

16. A compound according to claims 1 to 14, wherein the **S-C-connecting group** is a valence bond, –NH-C(=O)-, –NH-C(=O)-C_1-C_6 alkylene-, -S-S-, -S-S-C_1-C_6 alkylene-, -C(=O)-NH-(C_1-C_6 alkylene)-,

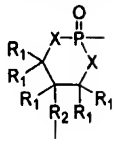


-NH-C(=O)-Arylene-$C(R^{16})_2$-NH-C(=O)-, where the right hand side of the formulae connects to the carrier.

17. A compound according to claims 1 to 14, wherein the **S-C-connecting group** is -S-S-, -C_1-C_6 alkylene-S-S -, -C(=O)-NH-(C_1-C_6 alkylene)-, -C(=O)-, or -C(=O)-Arylene-$C(R^{16})_2$-NR^{16}-C(=O)-, where the right hand side of the formulae connects to the carrier.

18. A compound according to claims 1 to 14, wherein the **S-C-connecting group** is -S-S-, -C(=O)-, or -C(=O)-Arylene-$C(R^{16})_2$-NR^{16}-C(=O)-, where the right hand side of the formulae connects to the carrier.

19. A compound according to claim 1 wherein the carrier is:



wherein R^2 is a valence bond or arylene.

20. A compound according to claims 1-19 where Complementing element is a nucleic acid.

21. A compound according to claims 1-19 where Complementing element is a sequence of nucleotides selected from the group of DNA, RNA, LNA PNA, morpholino derivatives or combinations thereof.

22. A library of compounds according to claim 1, wherein each different member of the library comprises a complementing element having a unique sequence of nucleotides, which identifies the functional entity.

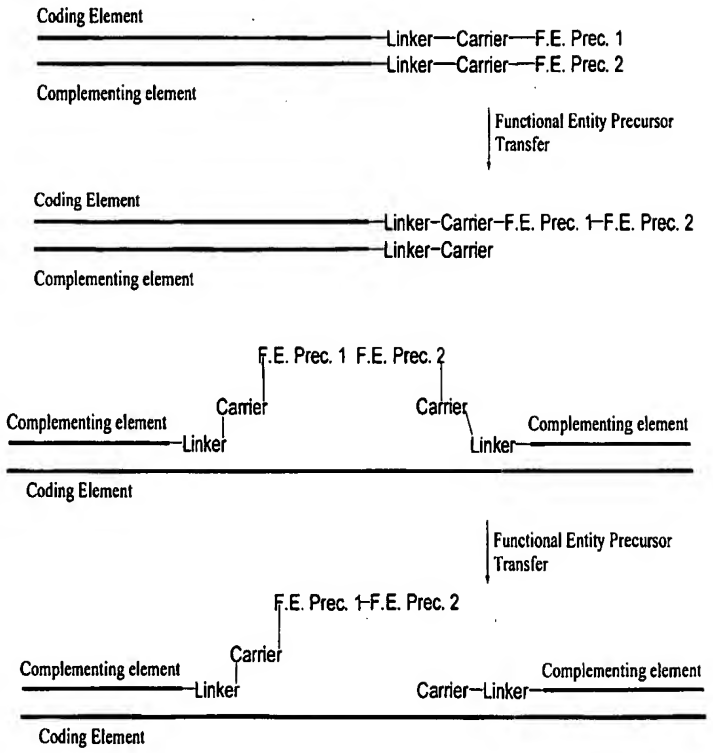
23. A method for transferring a Functional Entity Precursor to a recipient reactive group, comprising the steps of

providing one or more building blocks according to claims 1 to 21,

contacting the one or more building blocks with a corresponding encoding element associated with a recipient reactive group under conditions which allow for a recognition between the one or more complementing elements and the encoding elements, said contacting being performed prior to, simultaneously with, or subsequent to a transfer of the Functional Entity Precursor to the recipient reactive group.

24. The method according to claim 23, wherein the encoding element comprises one or more encoding sequences comprised of 1 to 50 nucleotides and the one or more complementing elements comprises a sequence of nucleotides complementary to one or more of the encoding sequences.

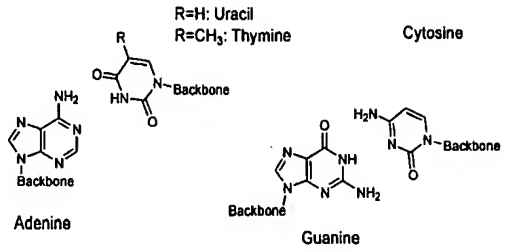
Figure 1. Two setups for Functional Entity Precursor Transfer



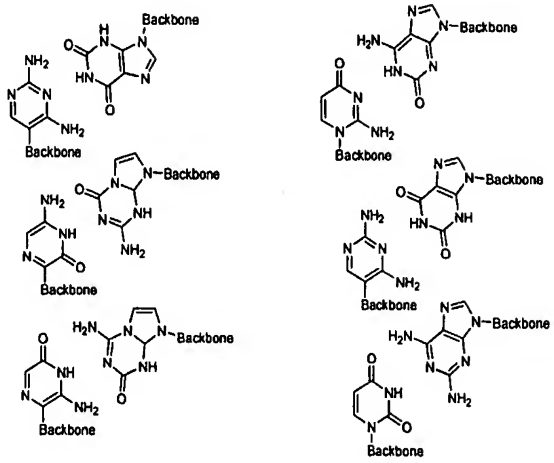
F.E. Prec. = Functional Entity Precursor

Figure 2. Examples of specific base pairing

Natural Base Pairs



Synthetic Base Pairs



Synthetic purine's base pairing with U/T or C

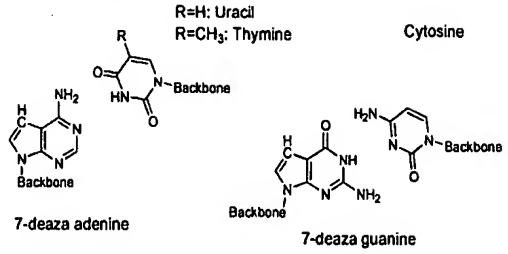


Figure 3. Example of non-specific base-pairing

I = Inosine

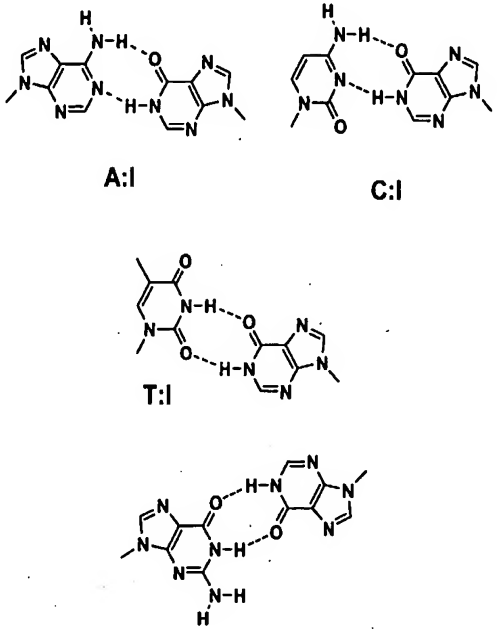


Figure 4. Backbone examples

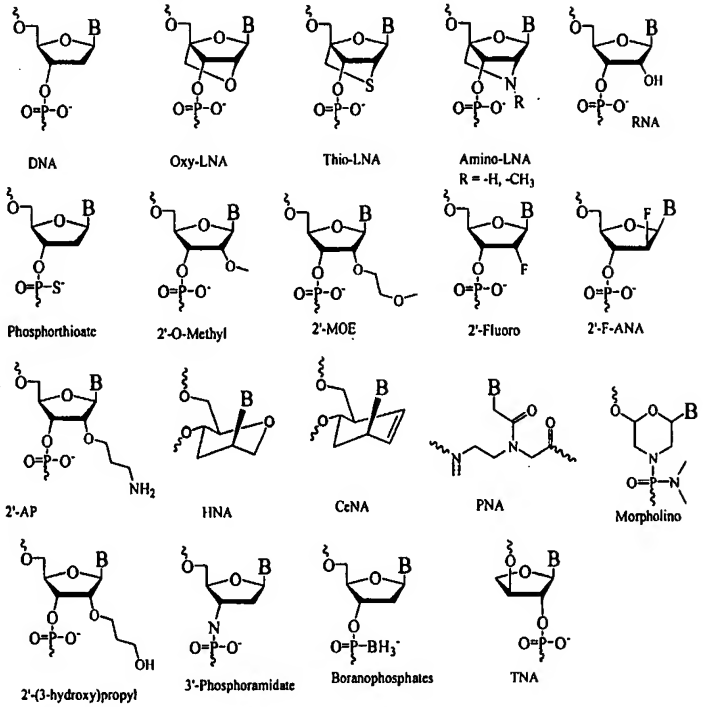
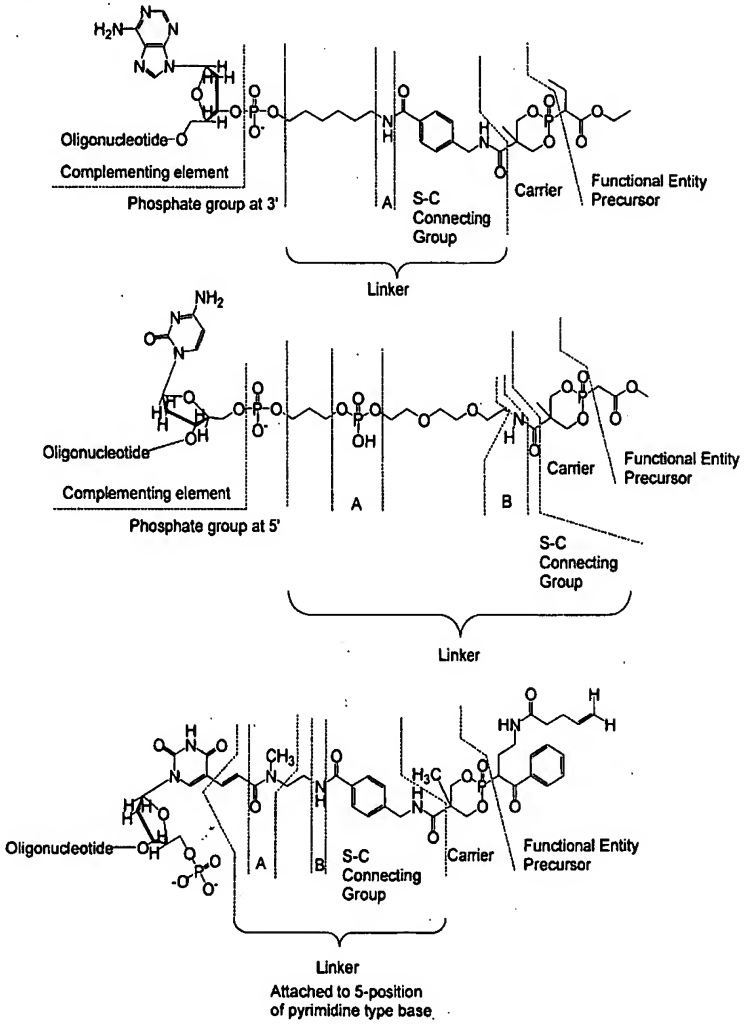


Figure 5.


Oligonucleotide
Complementing element
Phosphate group at 3'
A
S-C Connecting Group
Carrier
Functional Entity Precursor
Linker
Oligonucleotide
Complementing element
Phosphate group at 5'
A
B
Carrier
Functional Entity Precursor
S-C Connecting Group
Linker
Oligonucleotide
A
B
S-C Connecting Group
Carrier
Functional Entity Precursor
Linker
Attached to 5-position of pyrimidine type base